Desai, A.
09/830354

Priority date is Oct 28, 1998

FILE 'REGISTRY' ENTERED AT 09:15:19 ON 14 APR 2004
L1 5 S AMPA RECEPTOR ?/CN

L4 16 S (NITROGEN MUSTARD OR CHLORAMBUCIL OR MELPHALAN OR CYCLO
L5 16 S ("6-MERCAPTOPURINE" OR DOXORUBICIN OR DAUNORUBICIN OR D
L6 4843 S (PREDNISONE OR METHYLPREDNISOLONE OR INTERFERON? OR "IN
L7 4874 S L4 OR L5 OR L6

FILE 'HCAPLUS' ENTERED AT 09:23:07 ON 14 APR 2004
L1 5 SEA FILE=REGISTRY ABB=ON PLU=ON AMPA RECEPTOR ?/CN
L2 6039 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR AMPA(3A)RECEPTOR OR (ALPHA AMINO(1W)HYDROXY(1W)(METHYL OR ME)(1W)ISOXAZOL?)(5W)RECEPTOR
L3 73 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (CANCER? OR CARCIN? OR NEOPLAS? OR TUMOR OR TUMOUR OR ANTICANCER? OR ANTICARCIN? OR ANTINEOPLAS? OR ANTITUMOUR OR ANTITUMOR)
L4 16 SEA FILE=REGISTRY ABB=ON PLU=ON (NITROGEN MUSTARD OR CHLORAMBUCIL OR MELPHALAN OR CYCLOPHOSPHAMIDE OR BUSULFAN OR NITROSOUREA OR BCNU OR CCNU OR "METHYL-CCNU" OR ANTIMETABOLITE OR ANTIFOLATE OR PYRIMIDINE OR PURINE OR METHOTREXATE OR "5-FLUOROURACIL" OR AZATHIOPRINE OR CYTOSINE ARABINOSIDE OR "6-THIOGUANINE")/CN
L5 16 SEA FILE=REGISTRY ABB=ON PLU=ON ("6-MERCAPTOPURINE" OR DOXORUBICIN OR DAUNORUBICIN OR DAUNOMYCIN OR ACTINOMYCIN D OR BLEOMYCIN OR MITOXANTRONE OR NEOCARZINOSTATIN OR PROCARBAZINE OR MITOMYCIN C OR VINBLASTINE OR VINCRISTINE OR ETOPOSIDE OR CISPLATIN OR CARBOPLATIN OR DACARBAZINE OR CORTICOSTEROID OR PREDNISONE)/CN
L6 4843 SEA FILE=REGISTRY ABB=ON PLU=ON (PREDNISONE OR METHYLPREDNISOLONE OR INTERFERON? OR "INTERFERON-A"? OR "INTERFERON-B"? OR "INTERFERON-Γ"? OR INTERLEUKIN?)/CN
L7 4874 SEA FILE=REGISTRY ABB=ON PLU=ON L4 OR L5 OR L6
L8 8 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (NITROGEN MUSTARD OR CHLORAMBUCIL OR MELPHALAN OR CYCLOPHOSPHAMIDE OR BUSULFAN OR NITROSOUREA OR BCNU OR CCNU OR ANTIMETABOLITE OR ANTIFOLATE OR PYRIMIDINE OR PURINE OR METHOTREXATE OR FLUOROURACIL OR FLUORO URACIL OR AZATHIOPRINE OR AZATHIOPRINE OR CYTOSINE ARABINOSIDE)
L9 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (N MUSTARD OR CYCLO PHOSPHAMIDE OR BUSULPHAN OR NITROSO UREA OR ANTI(W)(METABOLITE OR FOLATE) OR THIO GUANINE OR THIOGUANINE)
L10 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (MERCAPTOPURINE OR DOXORUBICIN OR DAUNORUBICIN OR DAUNOMYCIN OR ACTINOMYCIN OR BLEOMYCIN OR MITOXANTRONE OR NEOCARZINOSTATIN OR PROCARBAZINE OR MITOMYCIN OR VINBLASTINE OR VINCRISTINE OR ETOPOSIDE OR CISPLATIN OR CARBOPLATIN OR DACARBAZINE OR CORTICOSTEROID OR PREDNISONE)
L11 18 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (PREDNISONE OR METHYLPREDNISOLONE OR (ME OR METHYL)(W)PREDNISOLONE OR INTERFERON OR IFN OR IL1 OR IL2 OR IL3 OR IL4 OR IL5 OR IL6 OR IL7 OR (IL OR INTERLEUKIN)(W)(1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR I) OR ILI OR IFNA? OR IFNB? OR IFNG?)

Claim 39

Searcher : Shears 571-272-2528

L12 15 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (L7 OR IRRADIAT? OR HYPERTHERMIA OR HYPER THERMIA OR ALKYLAT? OR (INTERCAL AT? OR NATURAL)(5A)(DRUG OR PHARMACEUT?) OR FEVER)
L13 27 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 OR L9 OR L10 OR L11 OR L12

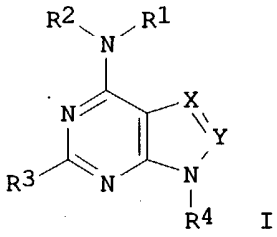
L13 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Feb 2004
ACCESSION NUMBER: 2004:89066 HCAPLUS
TITLE: Cell-specific pituitary gene expression profiles after treatment with leukemia inhibitory factor reveal novel modulators for proopiomelanocortin expression
AUTHOR(S): Abbud, Rula A.; Kelleher, Robert; Melmed, Shlomo
CORPORATE SOURCE: Department of Medicine, Division of Endocrinology, Cedars Sinai Research Institute, University of California School of Medicine, Los Angeles, CA, 90048, USA
SOURCE: Endocrinology (2004), 145(2), 867-880
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Leukemia inhibitory factor (LIF) mediates the hypothalamo-pituitary-adrenal stress response. Transgenic mice overexpressing LIF in the developing pituitary have altered pituitary differentiation with expansion of corticotropes, maintenance of Rathke's cleft cysts, and suppression of all other pituitary cell types. Affymetrix GeneChips were used to identify modulators of LIF effects in corticotrope (AtT-20) and somatolactotrope (GH3) cells. In addition to genes known to respond to LIF in corticotrope cells [e.g., suppressor of cytokine signaling-3 (SOCS-3), signal transducer and activator of transcription-3, SH2 domain-containing tyrosine phosphatase-1, and proopiomelanocortin (POMC)], corticotrope-specific changes were also observed for genes involved in glycolysis and gluconeogenesis, transcription factors, signaling mols., and expressed sequence tags. Two transcription factors identified, CCAAT/enhancer-binding protein β (C/EBPβ) and glial cell-derived neurotrophic factor (GDNF)-inducible factor (GIF), dose-dependently induced expression of the rat POMC promoter when overexpressed in AtT-20 cells. LIF further induced POMC transcription with C/EBPβ, but not with GIF. C/EBPβ also induced expression of the SOCS-3 promoter that was further enhanced by cotreatment with LIF. However, GIF did not affect SOCS-3 expression. These results indicate that C/EBPβ and GIF are downstream effectors of LIF corticotrope action. LIF also stimulates the expression of inhibitors of its actions, such as SOCS-3 and SH2 domain-containing tyrosine phosphatase-1. α2-HS-glycoprotein (AHSG)/fetuin, a secreted protein that antagonizes bone TGFβ/bone morphogenic protein signaling, was induced by LIF in a signal transducer and activator of transcription-3-dependent fashion. Pretreatment with AHSG/fetuin blocked LIF-induced expression of the POMC promoter independently of SOCS-3. Thus, using GeneChips, C/EBPβ and GIF have been identified as novel mediators and AHSG/fetuin as an inhibitor of LIF action in corticotropes.
IT INDEXING IN PROGRESS

IT **9001-99-4**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (5 precursor; cell-specific pituitary gene expression profiles after treatment with leukemia inhibitory factor reveal novel modulators for proopiomelanocortin expression as evaluated in AtT-20 and GH3 cells)
REFERENCE COUNT: 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

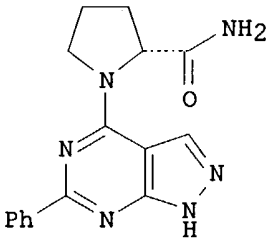
L13 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 25 Jul 2003
ACCESSION NUMBER: 2003:570644 HCAPLUS
DOCUMENT NUMBER: 139:133575
TITLE: Preparation of bicyclic pyrimidinyl derivatives as adenosine receptor ligands
INVENTOR(S): Castelhano, Arlindo L.; McKibben, Bryan
PATENT ASSIGNEE(S): OSI Pharmaceuticals Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 105 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003139427	A1	20030724	US 2002-227378	20020823

PRIORITY APPLN. INFO.: US 2002-227378 20020823
OTHER SOURCE(S): MARPAT 139:133575
GI



I



II

AB Title compds. I [Y = N, CR5 and X = N, CR6 wherein X, Y are both N or when Y = CR5, X = N or when X = CR6, Y = N; R1-2 = H, alkoxy, aminoalkyl, etc; R3-4 = H, alkyl, aryl, alkylaryl] are prepared For instance, 3-amino-4-carbamoylpyrazole is acylated with benzoyl chloride (Pyridine, 50°, 5-6 h), cyclized to the corresponding pyrazolopyrimidine (water, K2CO3, 100°, 16 h), converted to the chloride (POCl3, 106°, 2 h) and used for reactions with various amines to give the example compds., e.g., II. II has Ki = 76.7 nM for the adenosine A1 receptor, Ki = 242.7 nM for A2a and Ki = 1480.5 nM for A2b. I are useful for the treatment of.

L13 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 11 Jul 2003
ACCESSION NUMBER: 2003:532691 HCAPLUS
DOCUMENT NUMBER: 139:95435
TITLE: Modified receptors on cell membranes for the discovery of therapeutic ligands
INVENTOR(S): Schwartz, Thue W.; Martini, Lene; Heydorn, Arne; Jorgensen, Rasmus
PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055914	A2	20030710	WO 2002-DK900	20021220
WO 2003055914	A3	20031023		

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:		
DK 2001-1944	A	20011221
DK 2002-113	A	20020122
DK 2002-1043	A	20020703
US 2002-394122P	P	20020703

AB A drug discovery method is provided for selecting a compound selected from the group consisting of a small organic substance, a biopharmaceutical, or an antibody or part thereof. The method comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compound or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors comprises capturing one or more receptors on the exterior cell surface in a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a method comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor

internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely associated with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

IT **151662-26-9**, ITK kinase
RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(scaffolding protein used for membrane receptor interaction; modified receptors on cell membranes for the discovery of therapeutic ligands)

L13 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 20 Jun 2003
ACCESSION NUMBER: 2003:472692 HCAPLUS
DOCUMENT NUMBER: 139:19316
TITLE: Multiple binding moiety chromatography device, methods of using and methods of making same
INVENTOR(S): Wainer, Irving W.; Moaddel, Ruin; Cloix, Jean-Francois; Ertem, Goezen
PATENT ASSIGNEE(S): Rett Corporation, USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003050503	A2	20030619	WO 2002-US39349	20021210
WO 2003050503	A3	20031002		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003166301 A1 20030904 US 2002-315056 20021210

PRIORITY APPLN. INFO.: US 2001-337172P P 20011210

AB The present invention is directed to a chromatog. device with a stationary phase containing multiple binding moieties. The binding moieties are first solubilized and then immobilized on a stationary phase to create a multiple binding moieties phase for use in a chromatog. device. In an alternative to the stationary phase embodiment, a single binding moiety can be directly bonded covalently to a support within the chromatog. column. Combinations of constructions involving stationary phase immobilization and direct covalent bonding can also be employed. The multiple binding moiety chromatog. devices are useful in investigating interactions among different binding moieties in pharmacol. studies and in drug discovery.

L13 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

ED Entered STN: 13 Jun 2003

ACCESSION NUMBER: 2003:454117 HCAPLUS

DOCUMENT NUMBER: 139:36439

TITLE: Preparation of 2-pyridinone **AMPA** **receptor** antagonists for the treatment of demyelinating disorders and neurodegenerative diseases

INVENTOR(S): Smith, Terence

PATENT ASSIGNEE(S): Eisai Co., Ltd., Japan

SOURCE: PCT Int. Appl., 229 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003047577	A2	20030612	WO 2002-GB5542	20021206
WO 2003047577	A3	20030724		

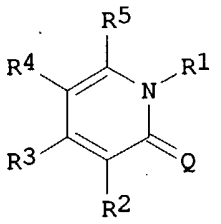
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

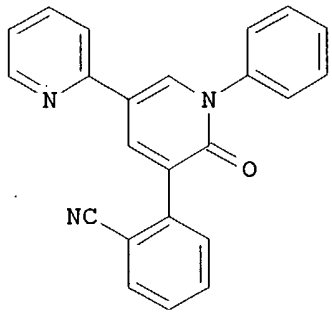
PRIORITY APPLN. INFO.: GB 2001-29260 A 20011206

OTHER SOURCE(S): MARPAT 139:36439

GI



I



II

AB Compns. comprising title compds. I [wherein Q = NH, O, or S; R1-R5 = independently H, halo, alkyl, or XA; X = a bond, O, S, CO, SO, SO2, NR6, NR7CO, CONR8, NR9CH2, CH2NR10, CH2CO, COCH2, NR11SO0-2, SO0-2NR12, CH2SO0-2, SO0-2CH2, CH2O, OCH2, NR13CONR14, NR15CSNR16, or (un)substituted alkylene, alkenylene, or alkynylene; A = (un)substituted cycloalkyl, cycloalkenyl, heterocyclyl, or (hetero)aryl; R6-R16 = independently H, alkyl, or alkoxy; with provisos; and salts and hydrates thereof] and an immunomodulatory, immunosuppressive, or an antiinflammatory agent are disclosed. Examples include the preparation of over 400 invention compds. and ten biol. assays. For instance, coupling of 5-(2-pyridyl)-3-bromo-2-methoxypyridine with 2-(2-cyanophenyl)-1,3,2-dioxaborinane in the presence of Cs2CO3 in DMF gave 3-(2-cyanophenyl)-5-(2-pyridyl)-2-methoxypyridine, which was converted to the 2(1H)-pyridone using NaI and TMSCl in MeCN. Reaction with a suspension of phenylboronic acid, Cu(OAc)2, and TEA in CH2Cl2 provided II. The latter in combination with **interferon** β reduced the severity of paralysis and weight loss during exptl. allergic encephalomyelitis (EAE) in rats compared to either II or **interferon** β alone. In addition, nearly 300 example compds. were tested and demonstrated suppressing action to calcium influx into nerve cells induced by AMPA with IC50 values ranging from 0.01 μM to 9.5 μM. Thus, I and compns. thereof are useful for the treatment of demyelinating disorders and neurodegenerative diseases.

IT **50-18-0, Cyclophosphamide 446-86-6,** Azothioprine **65271-80-9, Mitoxantrone 98530-12-2,** Viraferon **145155-23-3,** Betaseron **223378-40-3,** Alphaferone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(composition component; preparation of pyridinone **AMPA receptor** antagonists for treatment of demyelinating disorders and neurodegenerative diseases)

L13 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 27 May 2003
ACCESSION NUMBER: 2003:400445 HCAPLUS
DOCUMENT NUMBER: 139:51460
TITLE: **Interleukin-1**.beta. promotes oligodendrocyte death through glutamate excitotoxicity

AUTHOR(S): Takahashi, Jennifer L.; Giuliani, Fabrizio; Power, Christopher; Imai, Yoshinori; Yong, V. Wee
CORPORATE SOURCE: Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Can.
SOURCE: Annals of Neurology (2003), 53(5), 588-595
CODEN: ANNED3; ISSN: 0364-5134
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamate excitotoxicity is implicated in the progressive loss of oligodendrocytes in multiple sclerosis, but how glutamate metabolism is dysregulated in the disease remains unclear. Because there is microglia activation in all stages of multiple sclerosis, we determined whether a microglia product, **interleukin-1** β, could provide the mechanism for glutamate excitotoxicity. We found that whereas **interleukin-1**.beta. did not kill oligodendrocytes in pure culture, at produced apoptosis of oligodendrocytes in coculture with astrocytes and microglia. This requirement for a mixed glia environment suggests that **interleukin-1**.beta. impairs the well-described glutamate-buffering capacity of astrocytes. In support, antagonists at **AMPA**/kainate glutamate **receptors**, NBQX and CNQX, blocked the **interleukin-1**.beta. toxicity to oligodendrocytes. Another microglia/macrophage cytokine, **tumor** necrosis factor-α, also evoked apoptosis of oligodendrocytes in a mixed glia environment in an NBQX blockable manner. These results provide a mechanistic link between the persistent and insidious microglia activation that is evident in all stages of multiple sclerosis, with the recent appreciation that glutamate excitotoxicity leads to the destruction of oligodendrocytes in the disease.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 23 May 2003
ACCESSION NUMBER: 2003:396671 HCAPLUS
DOCUMENT NUMBER: 138:379256
TITLE: Cyclic prolylglycine composition and therapeutic uses
INVENTOR(S): Tran, Loi
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003041655	A2	20030522	WO 2002-US36639	20021112

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

US 2003109531 A1 20030612 US 2002-292732 20021112
PRIORITY APPLN. INFO.: NZ 2001-515432 A 20011113
US 2002-405909P P 20020826

AB The invention discloses compns. containing, and use of, cyclic prolylglycine, and analogs and mimetics thereof, as neuroprotective agents for the treatment and or prevention of neurol. disorders including but not limited to cerebral ischemia or cerebral infarction resulting from a range of phenomena, e.g. thromboembolic or hemorrhagic stroke, cerebral basospasms, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia (e.g. from drowning), pulmonary surgery, and cerebral trauma, as well as the treatment and prevention of chronic neurodenenerative disorders, e.g. Alzheimer's disease, Parkinson's disease, and Huntington's disease, and use as anticonvulsants.

L13 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 May 2003
ACCESSION NUMBER: 2003:376586 HCAPLUS
DOCUMENT NUMBER: 138:379245
TITLE: Cyclo(prolylglycine) and methods of use to treat neural disorders
INVENTOR(S): Guan, Jian; Gluckman, Peter David; Sieg, Frank
PATENT ASSIGNEE(S): Neuronz Limited, N. Z.; Neuronz Biosciences, Inc.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039487	A2	20030515	WO 2002-US36235	20021112
WO 2003039487	A3	20040115		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD,
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: NZ 2001-515371 A 20011109

NZ 2001-515432 A 20011113
NZ 2001-515551 A 20011116

AB Embodiments of pharmaceutical compns. comprising cyclo(Pro-Gly) (cPG) and methods for use in treating neural degeneration are provided. The cPG substantially prevents toxic neural degeneration and cell death and promotes neurite outgrowth in neurons, especially cerebellar neurons. The neuroprotective and neuroregenerative effects of cPG are useful to treat behavioral neurol. deficits involving motor control pathways.

IT **51-21-8**, 5-**Fluorouracil**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(5-**fluorouracil**-induced loss of Purkinje cells; cyclo(prolylglycine) for treatment of neural disorders)

IT **147-94-4**, **Cytosine arabinoside**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**cytosine arabinoside**-induced loss of Purkinje cells; cyclo(prolylglycine) for treatment of neural disorders)

L13 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 07 Feb 2003
ACCESSION NUMBER: 2003:97987 HCAPLUS
DOCUMENT NUMBER: 138:147750
TITLE: Composition and methods using tripeptide GPE and related compounds to improve neural outcome
INVENTOR(S): Gluckman, Peter David; Sirimanne, Ernest S.; Krissansen, Geoffrey W.; Kanwar, Jagat R.
PATENT ASSIGNEE(S): N. Z.
SOURCE: U.S. Pat. Appl. Publ., 18 pp., Cont.-in-part of U.S. Pat. Appl. 2002 13,277.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003027760	A1	20030206	US 2002-119386	20020408
CA 2178711	AA	19950629	CA 1994-2178711	19941220
EP 735894	A1	19961009	EP 1995-904702	19941220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09509404	T2	19970922	JP 1994-517338	19941220
AU 700838	B2	19990114	AU 1995-13281	19941220
AU 9513281	A1	19950710		
NZ 330758	A	20000526	NZ 1994-330758	19941220
US 2002013277	A1	20020131	US 2001-910461	20010720

PRIORITY APPLN. INFO.:
NZ 1993-250572 A 19931223
NZ 1994-260091 A 19940314
NZ 1994-264070 A 19940722
WO 1994-NZ143 W 19941220
US 1996-656331 B1 19960614
US 1997-907918 B1 19970811

US 2001-910461 A2 20010720
NZ 1994-277891 A1 19941220

AB A method is disclosed for protecting white matter, axons, and oligodendrocytes of a mammal, especially a human, against degeneration and death resulting from multiple sclerosis or periventricular leucomalacia by increasing the effective concentration of a GPE (Gly-Pro-Glu)-related compound in the central nervous system of the mammal. This increase may be achieved by administration to the mammal of an effective amount of a GPE-related compound, a prodrug thereof, or an implant containing cells that express the GPE-related compound or prodrug. The invention also discloses the use of a GPE-related compound, a prodrug thereof, or an implant containing cells that express the GPE-related compound or prodrug in the manufacture of a medicament for protecting white matter, axons, and oligodendrocytes of a mammal, especially a human, against degeneration and death resulting from multiple sclerosis or periventricular leucomalacia. Further disclosed are compns. containing a GPE-related compound, a prodrug thereof, or an implant containing cells that express the GPE-related compound or prodrug for protecting white matter, axons, and oligodendrocytes of a mammal, especially a human, against degeneration and death resulting from multiple sclerosis or periventricular leucomalacia.

L13 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 31 Jan 2003
ACCESSION NUMBER: 2003:76983 HCAPLUS
DOCUMENT NUMBER: 138:148639
TITLE: Comparison of protein or gene expression patterns of blood cells obtained by microarray to injury database to assess injury
INVENTOR(S): Sharp, Frank R.; Tang, Yang; Lu, Aigang
PATENT ASSIGNEE(S): University of Cincinnati, USA
SOURCE: PCT Int. Appl., 126 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003008647	A2	20030130	WO 2001-US44278	20011128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003104393	A1	20030605	US 2001-996275	20011128

PRIORITY APPLN. INFO.: US 2000-253568P P 20001128
AB Methods of injury assessment in an individual include the steps of

determining a pattern of expression exhibited by blood cells obtained from an individual and comparing the pattern of expression exhibited by the obtained blood cells to an injury database to assess the injury. The injury database includes genomic injury databases, proteomic injury databases, organ specific injury database, disease specific injury database. The patterns of gene or protein expression are obtained by microarray and analyzed by statistical anal., class prediction, clustering, and computer programs. The genes in the pattern of gene expression comprise acidosis-induced genes, hypoxia-induced genes, glucose-induced genes, ischemia-induced genes. The invention relates to sequences of two human genes which are expressed more highly in Parkinson's individuals. The invention also relates to genes associated with status epilepticus, hypoglycemia, ischemic stroke and hemorrhagic stroke in rat model. The invention also relates to gene expression pattern in males and females, resp. The invention also relates to assessing Parkinson's disease, stroke profusion, drug, neurofibromatosis, manic bipolar depression, migraine headache, schizophrenia, and Tourettes disease based on pattern of expression.

IT **186322-81-6**, ICE-like cysteine protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for, induction of, in response to stroke in rat; comparison of protein or gene expression patterns of blood cells obtained by microarray to injury database to assess injury)

L13 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 05 Jan 2003
ACCESSION NUMBER: 2003:6165 HCAPLUS
DOCUMENT NUMBER: 138:83349
TITLE: **Cancer** cell cell-surface molecule and **cancer**-specific promoter identification, targeting complexes, binding partners, and treatment methods
INVENTOR(S): Poulsen, Hans Skovgaard; Pedersen, Nina; Mortensen, Shila; Sorensen, Susanne Berg; Petersen, Mikkel Wandahl; Elsner, Henrik Irgang
PATENT ASSIGNEE(S): Odin Medical A/S, Den.
SOURCE: PCT Int. Appl., 223 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000928	A2	20030103	WO 2002-IB3534	20020619

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,

SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 2001-992 A 20010625
US 2001-301818P P 20010702

AB The invention describes methods for identification of mols. expressed at a different level on the cell surface of **cancer** cells compared to non-malignant cells and methods of identification of **cancer**-specific promoters to be used singly or in combination for delivery and expression of therapeutic genes for treatment of **cancer**. The invention furthermore describes targeting complexes targeted to cell surface mols. identified by the methods of the invention. In embodiments of the invention, the targeting complexes comprise the promoters identified by the methods of the invention. In addition the invention describes methods of identifying binding partners for the cell surface mols. and the binding partners per se. Methods of treatment using the targeting complexes and uses of the targeting complexes for the preparation of a medicament are also disclosed by the invention. Furthermore, the invention describes uses of the cell surface mols. or fragments thereof for preparation of vaccines.

IT **186322-81-6**, Caspase
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(apoptosis inducer; **cancer** cell cell-surface mol. and **cancer**-specific promoter identification, targeting complexes, binding partners, and treatment methods)

IT **50-76-0**, **Actinomycin** D **33419-42-0**, **Etoposide**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**cancer** cell cell-surface mol. and **cancer**-specific promoter identification, targeting complexes, binding partners, and treatment methods)

L13 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Dec 2002
ACCESSION NUMBER: 2002:919721 HCAPLUS
DOCUMENT NUMBER: 138:362306
TITLE: The DNA damaging agent **etoposide** activates a cell survival pathway involving α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors and mitogen-activated protein kinases in hippocampal neurons
AUTHOR(S): Lu, Chengbiao; Fu, Weiming; Zhao, Daohong; Mattson, Mark P.
CORPORATE SOURCE: Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD, 21224, USA
SOURCE: Journal of Neuroscience Research (2002), 70(5), 671-679
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Etoposide**, an inhibitor of topoisomerase II that induces DNA damage and can trigger cell death, is used as a chemotherapeutic agent. Because chemotherapies can result in neurol. complications

and because DNA damage in neurons is implicated in the pathogenesis of several neurodegenerative disorders, we studied the effects of **etoposide** on cultured hippocampal neurons. We found that **etoposide** induces neuronal apoptosis and that, prior to the cell death commitment point, there is an increase in whole-cell α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-induced current but no change in N-methyl-D-aspartate (NMDA)-induced current. Associated with the increase in AMPA-induced current was an increase in the amts. of **AMPA receptor** subunits GluR1 and GluR4, whereas levels of the NMDA receptor subunit NR1 were unaffected by **etoposide**. **AMPA receptor** activation can result in excitotoxic cell death but can also activate signaling pathways that promote synaptic plasticity and cell survival. We found that **etoposide** increases the activation of p42 and p44 mitogen-activated protein (MAP) kinases, and that activation of the MAP kinases by **etoposide** requires **AMPA receptor** activation. Pharmacol. blockade of **AMPA receptors** and p42/p44 MAP kinases, but not of NMDA receptors, exacerbated **etoposide**-induced cell death. These findings suggest that, although **etoposide** is neurotoxic, it also activates a cell survival pathway involving **AMPA receptor**-mediated activation of p42/p44 MAP kinases. Agents that selectively inhibit the cell life or death pathways triggered by DNA damage may prove useful in the settings of **cancer** and neurodegenerative disorders, resp.

IT **33419-42-0, Etoposide**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(the DNA damaging agent **etoposide** activates a cell survival pathway involving **AMPA receptors** and mitogen-activated protein kinases in hippocampal neurons)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 03 Oct 2002
ACCESSION NUMBER: 2002:750523 HCAPLUS
DOCUMENT NUMBER: 137:273218
TITLE: Combination preparation for prophylaxis and/or therapy of nerve cell damage and/or glial cell damage
INVENTOR(S): Sendtner, Michael; Sedlacek, Hans-Harald
PATENT ASSIGNEE(S): Medinnova Gesellschaft fur Medizinische Innovationen aus Akademischer Forschung m.b.H., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

DE 10113513 A1 20021002 DE 2001-10113513 20010320
WO 2002089779 A2 20021114 WO 2002-DE1049 20020319
WO 2002089779 A3 20030821
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2001-10113513 A 20010320

AB The invention provides a product containing at least one kinase inhibitor (A) that exhibits little or no inhibitory activity for Raf; and at least one neurotrophic factor (B); and/or at least one substance (C) which is able to intensify cell development and/or the release of one or several neurotrophic factors (B), as a combination preparation for the prophylaxis and/or therapy of nerve cell and/or glial cell damage.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 17 Feb 2002
ACCESSION NUMBER: 2002:124132 HCAPLUS
DOCUMENT NUMBER: 136:293274
TITLE: Varied actions of proinflammatory cytokines on excitotoxic cell death in the rat central nervous system
AUTHOR(S): Allan, Stuart M.
CORPORATE SOURCE: School of Biological Sciences, University of Manchester, Manchester, M13 9PT, UK
SOURCE: Journal of Neuroscience Research (2002), 67(4), 428-434
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin (**IL**)-**1**.beta. mediates diverse forms of neurodegeneration and exacerbates cell death induced by striatal injection of the excitotoxin α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) in the rat brain. The objective of this study was to determine whether this effect was specific to **IL-1**.beta.. Injection of **IL-1** α and AMPA in the striatum had effects identical to those of **IL-1**.beta., whereas coinjection of **IL-6** or **tumor** necrosis factor (TNF)-α with AMPA failed to induce significant cortical cell death. In contrast to **IL-1**.alpha., **IL-1**.beta., and **IL-6**, TNFα significantly reduced (by 38%) the local striatal damage. These findings suggest that the effect of **IL-1** on **AMPA receptor**

-mediated cell death in the rat striatum is not mimicked by other proinflammatory cytokines. Furthermore, TNFα shows neuroprotective effects against acute excitotoxic injury.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 28 Sep 2001
ACCESSION NUMBER: 2001:712142 HCAPLUS
DOCUMENT NUMBER: 136:35557
TITLE: Distinctive molecular profiles of high-grade and low-grade gliomas based on oligonucleotide microarray analysis
AUTHOR(S): Rickman, David S.; Bobek, Miroslav P.; Misek, David E.; Kuick, Rork; Blaivas, Mila; Kurnit, David M.; Taylor, Jeremy; Hanash, Samir M.
CORPORATE SOURCE: Departments of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, 48109, USA
SOURCE: Cancer Research (2001), 61(18), 6885-6891
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Astrocytomas are heterogeneous intracranial glial **neoplasms** ranging from the highly aggressive malignant glioblastoma multiforme (GBM) to the indolent, low-grade pilocytic astrocytoma. We have investigated whether DNA microarrays can identify gene expression differences between high-grade and low-grade glial **tumors**. We compared the transcriptional profile of 45 astrocytic **tumors** including 21 GBMs and 19 pilocytic astrocytomas using oligonucleotide-based microarrays. Of the .apprx.6800 genes that were analyzed, a set of 360 genes provided a mol. signature that distinguished between GBMs and pilocytic astrocytomas. Many transcripts that were increased in GBM were not previously associated with gliomas and were found to encode proteins with properties that suggest their involvement in cell proliferation or cell migration. Microarray-based data for a subset of genes was validated using real-time quant. reverse transcription-PCR. Immunohistochem. anal. also localized the protein products of specific genes of interest to the **neoplastic** cells of high-grade astrocytomas. Our study has identified a large number of novel genes with distinct expression patterns in high-grade and low-grade gliomas.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 03 Aug 2001
ACCESSION NUMBER: 2001:561199 HCAPLUS
DOCUMENT NUMBER: 138:231329
TITLE: Glutamate antagonists limit **tumor** growth. [Erratum to document cited in CA135:205098]
AUTHOR(S): Rzeski, Wojciech; Turski, Lechoslaw; Ikonomidou,

Chrysanthy
CORPORATE SOURCE: Department of Pediatric Neurology, Children's Hospital, Humboldt University, Berlin, D-13353, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(15), 8921
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The current affiliation of Lechoslaw Turski (Solvay Pharmaceuticals Research Labs., C. J. van Houteniaan 36, 1381 CP Weesp, The Netherlands) was inadvertently included in the list of author affiliations. The correct lists of authors, affiliations, and author footnotes are given.
IT **50-18-0, Cyclophosphamide**
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists limit **tumor** growth (Erratum))

L13 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 15 Jul 2001
ACCESSION NUMBER: 2001:508585 HCAPLUS
DOCUMENT NUMBER: 135:225196
TITLE: Gene expression analysis in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice model of Parkinson's disease using cDNA microarray: effect of R-apomorphine
AUTHOR(S): Grunblatt, Edna; Mandel, Silvia; Maor, Gila; Youdim, Moussa B. H.
CORPORATE SOURCE: Technion Faculty of Medicine, Bruce Rappaport Family Research Institute, Department of Pharmacology, Eve Topf and US National Parkinson's Foundation Centers for Neurodegenerative Diseases, Haifa, Israel
SOURCE: Journal of Neurochemistry (2001), 78(1), 1-12
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To establish the possible roles of oxidative stress, inflammatory processes and other unknown mechanisms in neurodegeneration, we investigated brain gene alterations in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mice model of Parkinson's disease using Atlas mouse cDNA expression array membrane. The expression of 51 different genes involved in oxidative stress, inflammation, glutamate and neurotrophic factors pathways as well as in still undefined processes, such as cell cycle regulators and signal transduction mols., was differentially affected by the treatment. The present study indicates the involvement of an addnl. cascade of events that might act in parallel to oxidative stress and inflammation to converge eventually into a common pathway leading to neurodegeneration. The attenuation of these gene changes by R-apomorphine, an iron chelator-radical scavenger drug, supports our previous findings in vivo where R-apomorphine was neuroprotective.

IT **122191-40-6**, Interleukin-converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression anal. in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice model of Parkinson's disease using cDNA microarray and effect of R-apomorphine)
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

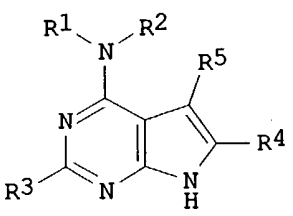
L13 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 08 Jun 2001
ACCESSION NUMBER: 2001:416773 HCAPLUS
DOCUMENT NUMBER: 135:46190
TITLE: Synthesis and use of substituted pyrrolo[2,3-b] **pyrimidines** as selective adenosine A1, A2a and A3 receptor antagonists
INVENTOR(S): Castelhano, Arlindo L.; McKibben, Bryan; Witter, David J.
PATENT ASSIGNEE(S): Osi Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 368 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001039777	A1	20010607	WO 2000-US32702	20001201
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6686366	B1	20040203	US 1999-454075	19991202
EP 1246623	A1	20021009	EP 2000-988011	20001201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003519102	T2	20030617	JP 2001-541509	20001201

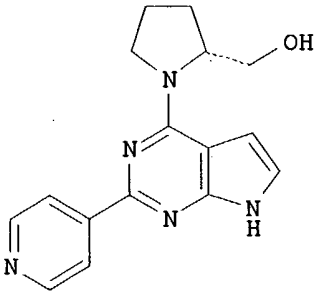
PRIORITY APPLN. INFO.:

US 1999-454074	A	19991202
US 1999-454075	A	19991202
US 1999-454254	A	19991202
US 1998-87702P	P	19980602
US 1999-123216P	P	19990308
US 1999-126527P	P	19990326
WO 1999-US12135	A2	19990601
WO 2000-US32702	W	20001201

OTHER SOURCE(S): MARPAT 135:46190
GI



I



III

AB The synthesis of compds. I, their binding to adenosine receptors and use are described [wherein; R1, R2 = H, (un)substituted alkyl or NR1R2 = (un)substituted 4-8 membered ring; R3 = (un)substituted 4-6 membered (aromatic) ring; R4, R5 = H, (un)substituted alkyl, aryl (with some exceptions)]. Over 100 examples are provided. Intermediate 4-chloro-7H-pyrrolo[2,3-d]**pyrimidines** were prepared by several routes from appropriately substituted cyano-pyrroles. Thus, 4-chloro-2-(4-pyridyl)-7H-pyrrolo[2,3-d]**pyrimidine** hydrochloride was reacted with D-prolinol (2.3 mol equiv) in DMSO at 120°C for 18 h to yield III in 13% yield after purification Compound I [R1 = AcNHCH2CH2; R2 = H; R3 = Ph; R4, R5 = Me; II] exhibited selective binding to adenosine receptor A1 with IC50 = 82.8 nM. Compound II also had Ki = 9.8 nM (vs. Ki = 7.1 for control ligand 8-cyclopentyl-1,3-dipropylxanthine (DPCPX)). **Pyrimidine** III binds 5 times more selectively to adenosine receptor A2a than A1, A2b or A3 (no data). Compound I [R1 = AcNH(CH2)4; R2 = H; R3 = Ph; R4, R5 = Me] is 10 times more selective for A3 than the other receptor subtypes. ClogP (calculated partition coefficient between octanol and H2O) values were determined for selected example compds. Claimed uses of I includes administration of a systemic formulation (i.e. ophthalmic) for the treatment of a disease associated with A1, A2a, and A3 adenosine receptors in a subject.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 05 Jun 2001
ACCESSION NUMBER: 2001:401743 HCAPLUS
DOCUMENT NUMBER: 135:205098
TITLE: Glutamate antagonists limit **tumor** growth
AUTHOR(S): Rzeski, Wojciech; Turski, Lechoslaw; Ikonomidou, Chrysanthy
CORPORATE SOURCE: Department of Pediatric Neurology, Children's Hospital, Charite-Virchow, Humboldt University, Berlin, D-13353, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(11),

6372-6377
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Neuronal progenitors and **tumor** cells possess propensity to proliferate and to migrate. Glutamate regulates proliferation and migration of neurons during development, but it is not known whether it influences proliferation and migration of **tumor** cells. We demonstrate that glutamate antagonists inhibit proliferation of human **tumor** cells. Colon adenocarcinoma, astrocytoma, and breast and lung **carcinoma** cells were most sensitive to the antiproliferative effect of the N-methyl-D-aspartate antagonist dizocilpine, whereas breast and lung **carcinoma**, colon adenocarcinoma, and neuroblastoma cells responded most favorably to the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate antagonist GYK152466. The antiproliferative effect of glutamate antagonists was Ca2+ dependent and resulted from decreased cell division and increased cell death. Morphol. alterations induced by glutamate antagonists in **tumor** cells consisted of reduced membrane ruffling and pseudopodial protrusions. Furthermore, glutamate antagonists decreased motility and invasive growth of **tumor** cells. These findings suggest **anticancer** potential of glutamate antagonists.

IT **50-18-0, Cyclophosphamide**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists limit **tumor** growth)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 12 Apr 2001
ACCESSION NUMBER: 2001:260108 HCAPLUS
DOCUMENT NUMBER: 136:144743
TITLE: Caspase-Mediated Suppression of Glutamate (**AMPA**) **Receptor** Channel Activity in Hippocampal Neurons in Response to DNA Damage Promotes Apoptosis and Prevents Necrosis: Implications for Neurological Side Effects of **Cancer** Therapy and Neurodegenerative Disorders
AUTHOR(S): Lu, Chengbiao; Fu, Weiming; Mattson, Mark P.
CORPORATE SOURCE: Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD, 21224, USA
SOURCE: Neurobiology of Disease (2001), 8(2), 194-206
CODEN: NUDIEM; ISSN: 0969-9961
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB DNA damage in neurons is implicated in the pathogenesis of several neurodegenerative disorders and may also contribute to the often severe neurol. complications in **cancer** patients treated with chemotherapeutic agents. DNA damage can trigger apoptosis, a

form of controlled cell death that involves activation of cysteine proteases called caspases. The excitatory neurotransmitter glutamate plays central roles in the activation of neurons and in processes such as learning and memory, but over activation of ionotropic glutamate receptors can induce either apoptosis or necrosis. Glutamate **receptors** of the **AMPA** (α-amino-3-hydroxy-5-methylisoxazole-4-propionate) type mediate such physiol. and pathol. processes in most neurons. We now report that DNA damage can alter glutamate receptor channel activity by a mechanism involving activation of caspases. Whole-cell patch clamp analyses revealed a marked decrease in AMPA-induced currents after exposure of neurons to camptothecin, a topoisomerase inhibitor that induces DNA damage; N-methyl-D-aspartate (NMDA)-induced currents were unaffected by camptothecin. The decrease in AMPA-induced current was accompanied by a decreased calcium response to AMPA. Pharmacol. inhibition of caspases abolished the effects of camptothecin on AMPA-induced current and calcium responses, and promoted excitotoxic necrosis. Combined treatment with glutamate receptor antagonists and a caspase inhibitor prevented camptothecin-induced neuronal death. Caspase-mediated suppression of AMPA currents may allow neurons with damaged DNA to withdraw their participation in excitatory circuits and undergo apoptosis, thereby avoiding widespread necrosis. These findings have important implications for treatment of patients with **cancer** and neurodegenerative disorders. (c) 2001 Academic Press.

IT **186322-81-6,** Caspase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(caspase-mediated suppression of **AMPA receptor** channel activity in hippocampus in response to DNA damage promotes apoptosis and prevents necrosis)

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 02 Mar 2001
ACCESSION NUMBER: 2001:152834 HCAPLUS
DOCUMENT NUMBER: 134:203457
TITLE: Cloning and characterization of rat Gas1 gene and its therapeutic application
INVENTOR(S): Luyten, Walter Herman Maria Louis; Naranjo, Jose Ramon; Mellstroem, Britt
PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001014549	A1	20010301	WO 2000-EP8182	20000821

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,

LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1212421	A1	20020612	EP 2000-962353	20000821
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003507067	T2	20030225	JP 2001-518862	20000821
NZ 516870	A	20031031	NZ 2000-516870	20000821
NO 2002000916	A	20020424	NO 2002-916	20020225

PRIORITY APPLN. INFO.: EP 1999-306702 A 19990824
WO 2000-EP8182 W 20000821

AB The invention clones rat Gas1 gene which encodes a membrane protein associated with the G0 phase of proliferative arrest and cell cycle exit in rat fibroblasts deprived of serum. Gas1 gene transfection into primary cultures of hippocampal neurons induces neuronal death, and Gas1 is involved in regulation of neuron death by excitotoxicity. The mechanism of Gas1 induced neuron death involves a purely apoptotic process and inhibition of the pro-caspase 9 or the effector caspases 3, 6 and 7 are involved in the death process triggered by Gas1. Mutational anal. of Gas1 protein demonstrates that the death-related domain in Gas1 is not RGD domain but the region encompassing amino acids 174 to 279. Blocking of translation of the Gas1 protein by its antisense oligonucleotide or antisense mRNA protects against excitotoxic death or death induced by staurosporine. A cellular model (NB69) with inhibited Gas1 gene expression by stable transfection of its antisense mRNA is established for making further stable cells for genes for lethal proteins such as mGluR-I to permit pharmacol. studies for drug screening.

IT **186322-81-6**, Caspase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cloning and characterization of rat Gas1 gene and therapeutic application)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 26 May 2000
ACCESSION NUMBER: 2000:351162 HCAPLUS
DOCUMENT NUMBER: 133:790
TITLE: New use of glutamate antagonists for the treatment of **cancer**
INVENTOR(S): Ikonomidou, Hrissanthi
PATENT ASSIGNEE(S): Germany
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1002535	A1	20000524	EP 1998-250380	19981028
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9964750	A1	20000515	AU 1999-64750	19991022
EP 1124553	A1	20010822	EP 1999-952622	19991022
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528415	T2	20020903	JP 2000-578005	19991022

PRIORITY APPLN. INFO.: EP 1998-250380 A 19981028
WO 1999-EP8004 W 19991022

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of **cancer**. Inhibitors of the interaction of glutamate with the **AMPA**, kainate, or NMDA **receptor** complexes are likely to be useful in treating **cancer** and can be formulated as pharmaceutical compns. They can be identified by appropriate screens.

IT **50-07-7, Mitomycin** C **50-18-0, Cyclophosphamide 50-44-2,** 6-**Mercaptopurine 50-76-0, Actinomycin** D **51-21-8,** 5-**Fluorouracil 53-03-2, Prednisone 55-86-7, Nitrogen mustard 55-98-1, Busulfan 57-22-7, Vincristine 59-05-2, Methotrexate 83-43-2, Methylprednisolone 120-73-0D, Purine,** analogs **147-94-4, Cytosine arabinoside 148-82-3, Melphalan 154-42-7,** 6-**Thioguanine 154-93-8, BCNU 289-95-2D, Pyrimidine,** analogs **305-03-3, Chlorambucil 446-86-6, Azathioprine 671-16-9, Procarbazine 865-21-4, Vinblastine 4342-03-4, Dacarbazine 9014-02-2, Neocarzinostatin 11056-06-7, Bleomycin 13010-20-3D, Nitrosourea,** derivs. **13010-47-4, CCNU 13909-09-6,** Methyl-**CCNU 15663-27-1, Cisplatin 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 33419-42-0, Etoposide 41575-94-4, Carboplatin 65271-80-9, Mitoxantrone**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutamate antagonists for **cancer** treatment, and combinations with other agents)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 14 Jan 2000
ACCESSION NUMBER: 2000:34733 HCAPLUS
DOCUMENT NUMBER: 132:88184
TITLE: Inhibitors of the interaction of glutamate with

the **AMPA** and/or kainate **receptor** complex for treatment of demyelinating disorders

INVENTOR(S): Turski, Lechoslaw; Smith, Terence
PATENT ASSIGNEE(S): Eisai Co., Ltd, Japan
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001376	A2	20000113	WO 1999-GB2112	19990702
WO 2000001376	A3	20010322		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1100504	A2	20010523	EP 1999-929545	19990702
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002519373	T2	20020702	JP 2000-557823	19990702

PRIORITY APPLN. INFO.: GB 1998-14380 A 19980702
GB 1998-24393 A 19981106
WO 1999-GB2112 W 19990702

AB New therapies can be devised based upon a demonstration of the role of glutamate in the pathogenesis of demyelinating disorders. Inhibitors of the interaction of glutamate with the **AMPA** and/or kainate **receptor** complex are likely to be useful in treating demyelinating disorders and can be formulated as pharmaceutical compns.

IT **50-18-0, Cyclophosphamide 446-86-6,** Azothioprine **65271-80-9,** Mitozantrone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of interaction of glutamate with **AMPA** and/or kainate **receptor** complex for treatment of demyelinating disorders, and use with other agents)

L13 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 02 Jun 1997
ACCESSION NUMBER: 1997:345622 HCAPLUS
DOCUMENT NUMBER: 127:32699
TITLE: HIV-1 Env and glutamate induction of NO, **IL1**, and TNF
AUTHOR(S): Merrill, Jean E.; Howard, Bruce D.; Maidment, Nigel T.
CORPORATE SOURCE: Department of Neurology, UCLA School of Medicine, Los Angeles, CA, 90024, USA
SOURCE: Molecular Signaling and Regulation in Glial Cells: A Key to Remyelination and Functional Repair, [International Symposium], Monastery Ohrbeck, Germany, Aug. 28-Sept. 2, 1995 (1997), Meeting Date 1995, 57-68. Editor(s): Jeserich,

Gunnar. Springer: Berlin, Germany.
CODEN: 64KKAE
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Several studies which have focused on CNS AIDS have implicated HIV-1 envelope (env) proteins in glutamate- and calcium-induced damage of neurons, most likely through nitric oxide (NO) induction. The authors have proposed that white matter damage, both to oligodendrocytes and myelin, could be mediated by NO, **IL-1**, and TNF in CNS AIDS and multiple sclerosis. In this study, the authors demonstrate that glutamate directly induces **IL-1**, TNF, and NO production in rat and human glial cell cultures. Furthermore, the authors show that HIV-1 env protein induction of the proinflammatory agents is glutamate-dependent. Addnl., gp160 and gp41 treatment of glia leads to an increased efflux and/or decreased uptake of aspartate/glutamate. The authors conclude that HIV-1 may alter the function of the glutamate transporter leading to an accumulation of extracellular glutamate and triggering of cytokine and NO production through the quisqualate receptor.

L13 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 14 Sep 1996
ACCESSION NUMBER: 1996:549049 HCAPLUS
DOCUMENT NUMBER: 125:212531
TITLE: Receptor interaction profile and CNS general pharmacology of metrifonate and its transformation product dichlorvos in rodents
AUTHOR(S): Hinz, Volker C.; Blokland, Arjan; van der Staay, Franz-Josef; Gebert, Irmingard; Schuurman, Teunis; Schmidt, Bernard H.
CORPORATE SOURCE: Inst. Neurobiol., Troponwerke GmbH & Co. KG, Cologne, Germany
SOURCE: Drug Development Research (1996), 38(1), 31-42
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study we assessed the possible effects of the putative Alzheimer therapeutič, metrifonate (39, 120, 390 μmol/kg), and its active transformation product, dichlorvos (4.5, 13.6, 45 μmol/kg), on the mammalian central nervous system (CNS). We did this by (1) investigating the receptor interaction profile of the two compds. in a range of in-vitro radioligand binding assays, and (2) by studying the acute compound effects in rats and mice using a battery of behavioral tests after a single oral administration. Metrifonate and dichlorvos failed to displace various radioligands from their resp. receptor binding sites on cell membranes at a concentration of 10 μM. In particular, there was no high-affinity interaction with muscarinic or nicotinic acetylcholine receptor binding in vitro. In the modified Irwin test (rat), both compds. induced transient cholinergic symptoms after oral administration of a single dose of 390 μmol/kg metrifonate and 13.6-45 μmol/kg dichlorvos. The observed symptoms, such as salivation, tremor, and diarrhea, lasted for up to 75 min. In the open field test (rat) metrifonate increased the number of rearings at all doses, whereas

dichlorvos had no effect on the parameters tested. Both compds. dose-dependently reduced the pentylenetetrazole threshold dose in mice. In this test, only the highest dose of metrifonate, but all doses of dichlorvos, caused a significant reduction of the convulsion threshold dose. Metrifonate and dichlorvos did not influence traction ability in mice. Metrifonate and dichlorvos did not influence hexobarbital-induced anesthesia in mice. Metrifonate induced hypothermia in rats only at the dose of 390 μmol/kg. Dichlorvos did not affect body temperature No analgesic potential was observed in the hot-plate test in mice. Furthermore, metrifonate and dichlorvos neither influenced motor coordination nor exhibited any cataleptic potential when administered to rats. Taken together, at cognition-enhancing doses, metrifonate (39-120 μmol/kg) is safe and well tolerated. The adverse symptoms observed at higher doses, together with the apparent lack of high-affinity interaction with neurotransmitter receptors in brain tissue and the similar profile of the active transformation product, dichlorvos, support the assumption that these compds. mediate a highly selective activation of the cholinergic system.

L13 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 22 Nov 1995
ACCESSION NUMBER: 1995:935538 HCAPLUS
DOCUMENT NUMBER: 124:27862
TITLE: HIV-1-derived neurotoxic factors: Effects on human neuronal cultures
AUTHOR(S): Gelbard, Harris A.; Dzenko, Kirk A.; Wang, Leo; Talley, Angela; James, Harold; Epstein, Leon
CORPORATE SOURCE: Medical Center, University Rochester, Rochester, NY, 14642, USA
SOURCE: Technical Advances in AIDS Research in the Human Nervous System, [Proceedings of an NIH Symposium on Technical Advances in AIDS Research in the Human Nervous System], Washington, D. C., Oct. 4-5, 1993 (1995), Meeting Date 1993, 61-71. Editor(s): Major, Eugene O.; Levy, Jay A. Plenum: New York, N. Y.
CODEN: 61ZRAL
DOCUMENT TYPE: Conference
LANGUAGE: English
AB HIV-1 infection of the developing central nervous system (CNS) results in a primary encephalopathy that is clin. devastating. Although it is established that HIV-1 productively infects brain microglia and macrophages, the mechanism(s) for neuronal dysfunction remain controversial. We have recently demonstrated that cocultures of HIV-1-infected monocytes and primary human fetal astrocytes secrete high, but variable levels of the cytokines **tumor** necrosis factor-α (TNF-a) and **interleukin-1** β (**IL-1**.beta.) relative to control uninfected monocyte plus astrocyte cocultures. Addnl., cocultures of HIV-1-infected monocytes and primary human fetal astrocytes secrete high levels of platelet-activating factor (PAF) (unpublished results). Both conditioned media from these cocultures and exogenous TNF-a, PAF, but not **IL-1**.beta. are neurotoxic to primary cultures of human fetal neurons. TNF-a-induced neurotoxicity is dose-dependent and can be blocked in

part by **AMPA receptor** antagonists. Studies suggest that the time course for this neurotoxicity is subacute, and occurs between 24-48 h in this cell culture system. Furthermore, PAF-induced neurotoxicity is dose-dependent and can be blocked in part by NMDA receptor antagonists. Other studies demonstrate that TNF-a and PAF down-regulate the expression of neurotransmitter receptors such as the dopamine D2 receptor, which may be dysfunctional in neuroAIDS. Taken together, these data suggest that TNF-a and PAF, produced by interactions between HIV-1-infected monocytes and astrocytes, may act as two candidate neurotoxins to produce neuronal dysfunction and death. Because these neurotoxins act in part through glutamate receptor systems, glutamate receptor antagonists may be useful in the pharmacotherapy of HIV-1-mediated encephalopathy.

L13 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 13 Nov 1993
ACCESSION NUMBER: 1993:601530 HCAPLUS
DOCUMENT NUMBER: 119:201530
TITLE: Cytokine stimulation increases intracellular calcium and alters the response to quisqualate in cultured cortical astrocytes
AUTHOR(S): Holliday, Janet; Gruol, Donna L.
CORPORATE SOURCE: The Scripps Research Institute, Department of Neuropharmacology, CVN 11, La Jolla, CA, 92037, USA
SOURCE: Brain Research (1993), 621(2), 233-41
CODEN: BRREAP; ISSN: 0006-8993
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cytokine levels are elevated in the central nervous system (CNS) in a variety of disorders and may contribute to abnormalities in CNS function associated with the disorders. To begin to understand the mechanisms through which elevated cytokines affect CNS cells, the authors examined the effects of cytokines on astrocyte physiol. within minutes of application as well as 24 h later. Both standard cultured cortical astrocytes and those induced to further differentiate by pre-treatment with forskolin were examined Such treated astrocytes may more closely resemble those in brains exhibiting elevated cytokine levels. The cytokine focused upon was **interleukin -1**.beta. (**IL-1**.beta.). Gamma-**interferon** (γ- **IFN**) and **tumor** necrosis factor-α (TNF-α) were also examined in some studies. Changes in calcium levels produced by acute application of these cytokines were measured. The most pronounced effect was an immediate calcium elevation in response to **IL-1** β in the forskolin pre-treated astrocytes. Longer term treatment with **IL-1**.beta. in forskolin pre-treated astrocytes enhanced the calcium response to quisqualate stimulation, a glutamate neurotransmitter receptor agonist. These results suggest that situations that cause chronic changes in cytokine levels and involve astrocytic differentiation, such as chronic CNS infection or Alzheimer's disease, could change astrocytic responses to normal stimuli. Such changes may result in altered astrocytic support of neurons and therefore cause changes in CNS function.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 09:37:15 ON 14 APR 2004)
L14 51 S L13
L15 33 DUP REM L14 (18 DUPLICATES REMOVED)

L15 ANSWER 1 OF 33 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004148180 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 15042683
TITLE: 5-**fluorouracil**-induced oligodendrocyte death and inhibitory effect of cycloheximide, Trolox, and Z-VAD-FMK in murine cortical culture.
AUTHOR: Cho Ki-Hyun; Choi Sung-Min; Kim Byeong-Chae; Lee Seung-Han; Park Man-Seok; Kim Myeong-Kyu; Kim Jong-Keun
CORPORATE SOURCE: Department of Neurology, Chonnam National University Medical School, Chonnam National University Research Institute of Medical Science, Gwangju, South Korea.
SOURCE: Cancer, (2004 Apr 1) 100 (7) 1484-90.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20040326
Last Updated on STN: 20040327

AB BACKGROUND: 5-**fluorouracil** (5-FU) is a widely used **anticancer** drug. One of the adverse effects of this drug is selective cerebral white matter injury, but to the authors' knowledge its mechanism has not been well documented. The current study was performed to investigate the mechanism of cerebral white matter injury caused by 5-FU and to develop the intervention to attenuate its injury in vitro. METHODS: Mixed oligodendrocyte/astrocyte cells were dissociated from specimens taken from approximately 2-day-old postnatal mouse cortex and cultured for 3-4 weeks. The culture cells were exposed to 5-FU, cycloheximide, emetine, Z-VAD-fmk, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(F)-quinoxaline (NBQX), Trolox, and epigallocatechin gallate. Oligodendrocyte cell death was assessed by counting the number of viable galactocerebroside-positive cells per x 100 field. RESULTS: Mixed oligodendrocyte/astrocyte culture cells that were exposed to 5-FU (at doses of 10 microM, 30 microM, and 100 microM) for 24 hours ensued concentration-dependent oligodendrocyte death. The majority of oligodendrocytes, but few astrocytes, were injured by 100 microM 5-FU. Trolox, a vitamin E analog antioxidant, as well as cycloheximide (a protein synthesis inhibitor) and Z-VAD-fmk (a caspase inhibitor), significantly attenuated the 5-FU-induced oligodendrocyte death. However, NBQX, an alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropionic acid (**AMPA**) **receptor** antagonist, did not appear to effect the 5-FU-induced oligodendrocyte death. CONCLUSIONS: The findings of the current study suggested that 5-FU led to oligodendrocyte death rather than astrocyte death by way of the apoptotic process, whereas antioxidants may prevent the 5-FU-induced oligodendrocyte cell death in vitro.

Copyright 2004 American Cancer Society.

L15 ANSWER 2 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-902924 [82] WPIDS
CROSS REFERENCE: 2003-229198 [22]
DOC. NO. CPI: C2003-256428
TITLE: Use of steroidal sapogenin derivatives in the preparation of compositions for treating e.g. non-cognitive neurodegeneration.
DERWENT CLASS: B01 D13
INVENTOR(S): GUNNING, P; HU, Y; ORSI, A; REES, D; XIA, Z
PATENT ASSIGNEE(S): (PHYT-N) PHYTOPHARM PLC
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003082893	A2	20031009	(200382)*	EN	30

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003082893	A2	WO 2003-GB1380	20030327

PRIORITY APPLN. INFO: WO 2002-GB1578 20020328; AR 2002-101170 20020327; US 2002-368178P 20020328
AN 2003-902924 [82] WPIDS
CR 2003-229198 [22]
AB WO2003082893 A UPAB: 20031223
NOVELTY - Use of one or more steroidal sapogenin derivatives (I)-(III) in the preparation of compositions for treating non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration, or receptor dysfunction or loss in the absence of cognitive, neural and neuromuscular impairment, is new.

DETAILED DESCRIPTION - Use of one or more steroidal sapogenin derivatives of formula (I)-(III), their stereoisomers, racemic mixtures, pro-drugs and/or salts (containing at least one X substituent; and the carbon atom at the 3-position, or in case of (II) and (III), the 3-position carbon and/or the 26-position carbon carries an O-sugar moiety in which sugar group is mono- to tri-saccharide) in the preparation of compositions for treating non-cognitive neurodegeneration, non-cognitive neuromuscular degeneration, motor-sensory neurodegeneration, or receptor dysfunction or loss in the absence of cognitive, neural and neuromuscular impairment, is new.

R1-R8, R10, R13, R18-R24, R26-R32, R34, R36, R37, R35a = T or =O;

T = H, OH, halo, MeS, MeSO, MeSO2, N3, NH2, MeSO2NH, alkyl, absent or OR;

R = alkyl or acyl;

R9, R11, R12, R15-R17, R25, R35 = T;

R14, R33 = T or alkyl;

R33a = T, =O or alkyl;

dotted line = optional double bond; and

X = halo, MeS, MeSO, MeSO2, N3, NH2, MeSO2NH- or alkyl;

provided that R25 in (III) is in beta -orientation.

ACTIVITY - Neuroprotective; CNS-Gen; Muscular-Gen.; Nootropic; Antiparkinsonian; Antidepressant; Neuroleptic; Ophthalmological; Anticonvulsant; Hypertensive; Vulnerary; Cerebroprotective; Tranquilizer; Antiinflammatory; Immunomodulator; Antidiabetic; Vasotropic; Cardiant; Antiasthmatic.

The neuroprotective effect of sarsasapogenin (Ia) was evaluated in aged Sprague-Dawley rats by administration of (Ia) (18 mg/kg/day) through food for 2-3 months. The learning and memory abilities were assessed by using a Y-maze apparatus and dopamine receptor density was assessed in the brain homogenate by the dual-site competitive ligand binding assay. The dopamine (D1/D2) receptor density was 157/200.6 fmol/mg protein in young rats (control 1); 129.2/153.8 fmol/mg protein in aged rats not receiving (Ia) (control 2); and 172/206.4 fmol/mg protein in aged rats receiving (Ia). In control 1/control 2/(Ia), muscarinic receptor density was 1000/875/1025 fmol/mg protein; and the learning and memory ability was 5.2/2/5.2 (no units), respectively. The results showed that (Ia) restored the dopamine and muscarinic receptors density as well as learning ability and memory in the aged rats by reversing the neuroimpairments.

MECHANISM OF ACTION - None given.

USE - For treating non-cognitive neurodegeneration; non-cognitive neuromuscular degeneration; motor-sensory neurodegeneration; and receptor dysfunction or loss in the absence of cognitive, neural and neuromuscular impairment (e.g. Parkinson's disease, postencephalitic Parkinsonism, depression, schizophrenia, muscular dystrophy (including facioscapulohumeral muscular dystrophy (FSH), Duchenne muscular dystrophy, Becker muscular dystrophy and Bruce's muscular dystrophy, Fuch's dystrophy, myotonic dystrophy, corneal dystrophy, reflex sympathetic dystrophy syndrome (RSDSA), neurovascular dystrophy), myasthenia gravis, Lambert Eaton disease, Huntington's disease, motor neuron diseases (including amyotrophic lateral sclerosis (ALS), multiple sclerosis), postural hypotension, traumatic neurodegeneration e.g. following stroke or following an accident (e.g. traumatic head injury or spinal cord injury), Batten's disease, Cockayne syndrome, Down syndrome, corticobasal ganglionic degeneration, multiple system atrophy, cerebral atrophy, olivopontocerebellar atrophy, dentatorubral atrophy, pallidoluysian atrophy, spinobulbar atrophy, optic neuritis, sclerosing pan-encephalitis (SSPE), attention deficit disorder, post-viral encephalitis, post-poliomyelitis syndrome, Fahr's syndrome, Joubert syndrome, Guillain-Barre syndrome, lissencephaly, Moyamoya disease, neuronal migration disorders, autistic syndrome, polyglutamine disease, Niemann-Pick disease, progressive multifocal leukoencephalopathy, pseudotumor cerebri, Refsum disease, Zellweger

syndrome, supranuclear palsy, Friedreich's ataxia, spinocerebellar ataxia type 2, Rhett syndrome, Shy-Drager syndrome, tuberous sclerosis, Pick's disease, chronic fatigue syndrome, neuropathies including hereditary neuropathy, diabetic neuropathy and mitotic neuropathy, prion-based neurodegeneration (including Creutzfeldt-Jakob disease (CJD), variant CJD, new variant CJD, bovine spongiform encephalopathy (BSE), GSS, FFI, kuru and Alper's syndrome), Joseph's disease, acute disseminated encephalomyelitis, arachnoiditis, vascular lesions of the central nervous system, loss of extremity neuronal function, Charcot-Marie-Tooth disease, susceptibility to heart failure, asthma, or macular degeneration) in human and non-human animals (claimed).

ADVANTAGE - The compounds are strongly neuroprotective, stimulative of neurite outgrowth, and preventive of neurotoxicity. The compounds slow or reverse decrease in cholinergic and dopamine receptor density. The compounds reverse the receptor loss effects, simultaneously reversing the deterioration towards the normal or young state with protection. The compounds reverse the apoptotic effect in the non-**neoplastic** domain of cell life.

Dwg.0/6

L15 ANSWER 3 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-558931 [52] WPIDS
DOC. NO. CPI: C2003-150571
TITLE: New deazapurine compounds useful for treating e.g. myocardial ischemia, bronchoconstriction or asthma.
DERWENT CLASS: B02
INVENTOR(S): CASTELHANO, A L; MCKIBBEN, B; WERNER, D S; WITTER, D
PATENT ASSIGNEE(S): (OSIP-N) OSI PHARM INC
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003048120	A2	20030612	(200352)*	EN	85

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2002360436 A1 20030617 (200419)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003048120	A2	WO 2002-US38055	20021127
AU 2002360436	A1	AU 2002-360436	20021127

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2002360436 A1 Based on WO 2003048120

PRIORITY APPLN. INFO: US 2001-337274P 20011130; US 2001-335273P 20011130

AN 2003-558931 [52] WPIDS

AB WO2003048120 A UPAB: 20030813

NOVELTY - Deazapurine compounds (I) or their salts are new.

DETAILED DESCRIPTION - Deazapurine compounds of formula (I) or their salts are new.

m = 0 - 3;

R2 = optionally substituted imidazole or pyrazole;

R5 = H, optionally substituted alkyl, aryl or alkylaryl; and

R7 = halo, 1-4C alkyl, OH, O-1-4C alkyl, NH2 or NH-(1-4C) alkyl.

INDEPENDENT CLAIMS are included for

(1) treating a disease associated with an A3 adenosine receptor in a subject involving administering (I);

(2) pharmaceutical composition containing (I) carrier and at least one of steroid, beta 2 agonist, glucocorticoid, a leukotriene antagonist or anticholinergic agonist;

(3) packaged pharmaceutical composition comprising a container holding (I) and instructions for using (I); and

(4) use of (I) for manufacturing a medicament for treating a disease associated with an A3 and A1 adenosine receptor.

ACTIVITY - Cardiant; Antiasthmatic; Ophthalmological; Vasotropic; Antiinflammatory; Respiratory; Antiallergic; Nootropic; Nephrotropic; Hypotensive; Antipyretic; Antipsoriatic; Dermatological; Cytostatic; Antiulcer; Antithyroid; Antiarthritic; Immunosuppressive; Antidiabetic; Neuroprotective; Antianemic; Antiinfertility; Diuretic.

MECHANISM OF ACTION - Adenosine A1 and A3 receptor inhibitor; Diuresis inducer.

Membrane from HEK293 cell was diluted in binding buffer (50 mM Tris-HCl, pH 7.4, containing 10 mM MgCl2, 1.0 mM EDTA, 0.25 % BSA, 2 U/ml adenosine deaminase and 1-protease inhibitor). Membranes were incubated with (125-I) AB-MECA (0.75 nM) in binding buffer at 25 deg. C for 1 hour in the presence of 3-(5,6-dimethyl-2-phenyl-7H-pyrrolo(2,3-d)pyrimidin-4-ylamino)-cyclopentanol (A). The assay was terminated, adenosine 3 receptor competition radioligand binding was calculated and (A) showed an IC50 of 1 nM.

USE - For treating disease associated with an A3 and A1 adenosine receptor e.g. antidiuresis, myocardial ischemia, bronchoconstriction, asthma, glaucoma, retinopathy, ocular ischemia, macular degeneration, respiratory disorder, inflammation or eye, bronchitis, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory disorder, memory disorder, congestive heart failure, renal failure, cardiac arrhythmia, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, cardiac hypoxia, hypertension (all claimed), cardiovascular disorder, hypersensitivity, hay **fever**, serum asthma, sickness, allergic vasculitis, atopic dermatitis, psoriasis, eczema, idiopathic pulmonary fibrosis, osinophilic chlorecystitis, chronic airway inflammation, hypereosinophilic syndromes, eosinophilic gastroenteritis, urticaria, eosinophilic myocardial disease, episodic angioedema, inflammatory bowel disease, ulcerative colitis,

allergic granulomatosis, **carcinomatosis**, neurological disorder, mental disorder, cognitive disorder, Crohn's disease, Grave's disease, arthritis, autoimmune disease, diabetes, multiple sclerosis, anemia, fertility disorders, lupus erythematosus, reperfusion injury, brain arteriole diameter and immunological disorder.

ADVANTAGE - (I) helps contraction of smooth muscle underlying respiratory epithelia, mast cell degranulation or eosinophil activity.

Dwg.0/0

L15 ANSWER 4 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-586811 [55] WPIDS
DOC. NO. CPI: C2003-158636
TITLE: Composition useful for the treatment of neurodegenerative disease e.g. encephalitis, multiple sclerosis comprises 1,2-dihydropyridine derivative and an immunomodulatory, immunosuppressive or an anti-inflammatory agent.
DERWENT CLASS: B03
INVENTOR(S): SMITH, T
PATENT ASSIGNEE(S): (EISA) EISAI CO LTD
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003047577	A2	20030612	(200355)*	EN	229

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2002347365 A1 20030617 (200419)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003047577	A2	WO 2002-GB5542	20021206
AU 2002347365	A1	AU 2002-347365	20021206

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002347365	A1 Based on	WO 2003047577

PRIORITY APPLN. INFO: GB 2001-29260 20011206
AN 2003-586811 [55] WPIDS
AB WO2003047577 A UPAB: 20030828
NOVELTY - A composition comprises 1,2-dihydropyridine derivative (I) and an immunomodulatory, immunosuppressive or an anti-inflammatory agent.

DETAILED DESCRIPTION - A composition comprises 1,2-dihydropyridine derivative of formula (I), its salt or hydrate and an immunomodulatory, immunosuppressive or an anti-inflammatory agent.

Q = NH, O or S;

R1 - R5 = H, halo, 1-6C alkyl or -X-A;

X = 1-6C alkylene, 2-6C alkenylene or 2-6C alkynylene (all optionally substituted) or T;

T = single bond, -O-, -S-, -CO-, -SO-, -SO2-, N(R6), -N(R7)-CO-, -CO-N(R8)-, -N(R9)-CH2-, -CH2-N(R10)-, -CH2-CO-, -CO-CH2-, N(R11)-S(O)m-, -S(O)n-N(R12)-, -CH2-S(O)p-, -S(O)q-CH2-, -CH2-O-, -O-CH2-, -NC(R13)CO-N(R14)- or -N(R15)-CS-N(R16);

R6 - R16 = H, 1-6C alkyl or 1-6C alkoxy

m, n, p, q = 0 - 2; and

A = 3-8C cycloalkyl, 3-8C cycloalkenyl, 5 - 14 membered non-aromatic heterocyclic group, 6-14C aromatic hydrocarbocyclic group or 5 - 14 membered aromatic heterocyclic group (all optionally substituted).

Provided that 3 groups of R1 - R5 are -X-A; and the residual 2 groups are H, halo or 1-6C alkyl. INDEPENDENT CLAIMS are included for the following:

(1) a kit comprising a container containing the composition and an another container containing an immunoregulatory or antiinflammatory agent, optionally with instructions for use; and

(2) a composition comprising 1,3,5-substituted pyridone compound of formula (III) and an immunoregulatory or an antiinflammatory agent.

A4, A5 = 6-14C aromatic hydrocarbocyclic group or 5 - 14-membered aromatic heterocyclic group (both optionally substituted); and

R = H or halo.

ACTIVITY - Neuroprotective; Antiinflammatory; Immunosuppressive; Nootropic; Antiparkinsonian; Anticonvulsant; Analgesic; Neuroleptic; Antiaddictive; Antiemetic; Ophthalmological; Virucide; Anti-HIV; Antibacterial. 3-(2-Cyanophenyl)-1-phenyl-5-(2-pyridyl)-1,2-dihydropyridin-2-one (A) was suspended in 0.5 % methyl cellulose solution to obtain concentration of 4 mg/ml. **Interferon**- beta was dissolved in phosphate buffer saline to obtain a concentration of 5 multiply 106 units/ml. Rats were dosed once daily on days 7 - 16 post immunization with either vehicle (methyl cellulose), (A) alone in the dose of 10 mg/kg, **interferon**- beta alone in dose of 1 multiply 106 units/rat, or (A) (10 mg/kg) combined with **interferon**- beta in the dose of 1 multiply 106 units/rat. (A) in combination with **interferon**- beta significantly reduced disease duration, and peak and cumulative disease score relative to vehicle, **interferon** B and the compound treatment alone.

MECHANISM OF ACTION - **alpha** -**Amino**-3-**hydroxy**-5-**methyl**-4-**isoxazole**-propinate (**AMPA**) and kainate **receptor** inhibitor.

The suppressing action of 3-(2-cyanophenyl)-1-phenyl-5-(2-pyridyl)-1,2-dihydropyridin-2-one (A) to calcium influx into nerve cells induced by AMPA was investigated using the primary culture systems of nerve cells of cerebral cortex of embryo of rat. (A) showed IC50 value of 0.1 micro M.

USE - In the manufacture of a medicament for prevention or

treatment of neurodegenerative disease including demyelinating disorder (e.g. encephalitis, acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, HIV-myelopathy, HTLV-myelopathy and progressive multifocal leucoencephalopathy); a secondary demyelinating disorder (e.g. CNS lupus erythematodes, polyarteritis nodosa, Sjoegren's syndrome and sarcoid granuloma isolated cerebral vasculitis) (all claimed); cerebral vascular accidents of acute stage, head injury, neuropathy by hypoxia or hypoglycemia; Alzheimer's disease; Parkinson's disease; Huntington's chorea; amyotrophic lateral sclerosis and spinocerebellar degeneration. Also for the treatment of epilepsy, hepatic encephalopathy, peripheral neuropathy, spastic paralysis, pain, neuralgia, schizophrenia, anxiety, drug abuse, nausea, vomiting, urinary, disturbance, visual disturbance due to glaucoma, auditory disturbance due to antibiotics, food poisoning, infection encephalomyelitis (e.g. cerebrospinal meningitis (e.g. HIV cerebrospinal meningitis)), cerebrovascular dementia, dementia and nervous symptoms due to meningitis.

ADVANTAGE - The composition suppresses the neurotoxicity, axonal toxicity and oligodendroglial toxicity of neurotransmitters and achieves a protective action.

Dwg.0/2

L15 ANSWER 5 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2003-482305 [45] WPIDS

DOC. NO. CPI: C2003-129020

TITLE: Protection, regeneration or repair of damaged neurons and glia cells to treat neurological disorders e.g. multiple sclerosis, Parkinson's disease involves administration of cyclic propyl glycine, its analog or peptidomimetic.

DERWENT CLASS: B05

INVENTOR(S): TRAN, L

PATENT ASSIGNEE(S): (TRAN-I) TRAN L

COUNTRY COUNT: 102

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003041655	A2	20030522	(200345)*	EN	19

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003041655	A2	WO 2002-US36639	20021112

PRIORITY APPLN. INFO: US 2002-405909P 20020826; NZ 2001-515432 20011113

AN 2003-482305 [45] WPIDS

AB WO2003041655 A UPAB: 20030716

NOVELTY - Protection, regeneration or repair of damaged neurons and glia cells due to injury or disease involves administration of cyclic propyl glycine (cPG), its analog or peptidomimetic.

ACTIVITY - Nootropic; Neuroprotective; Anticonvulsant; Antiparkinsonian; Cerebroprotective; Cardiant; Hemostatic; Immunosuppressive; Ophthalmological.

The neuroprotective activity was evaluated by using cerebellum tissue isolated from Wistar rats (postnatal day 4) were fixed on a slide forming microexplants. The microexplants were incubated and toxin (L-glutamate-100 mM in Millipore water) was applied simultaneously with cyclic propyl glycine (cPG) (test). cPG was administered at 6 hours after glutamate treatment. Control was maintained using a vehicle instead of cPG. After incubation, the count of neuronal cells found to be 4200/3800 for test/control respectively. The glutamate treatment resulted in 85% loss of cerebellum neurons whereas cPG significantly reduced the glutamate induced neuronal death.

MECHANISM OF ACTION - N-Methyl-D-aspartate (NMDA) Receptor Antagonist; **alpha -Amino**-3-**hydroxy**-5-**methyl** 4-**isoxazole** propionic Acid (**AMPA**) **Receptor** Antagonist; Antiapoptotic.

USE - The method is used for protecting, regenerating and repairing neurons and glia cells to treat neurotic cell death, neurodegenerative diseases (e.g. Alzheimer's disease, multiple sclerosis, Huntington's disease and Parkinson's disease), neurological injury (e.g. traumatic brain injury, stroke, cardiac artery bypass graft surgery, toxin and asphyxia), acute or chronic encephalomyelitis, optic neuritis, transverse myelitis, Devic's disease, leucodystrophies, progressive multifocal leukoencephalopathy, central pontine myelinolysis, neuromyelitits optica, diffuse cerebral sclerosis of Schilder, acute and subacute necrotizing haemorrhagic encephalitis; for preventing programmed cell death; for treating white matter damage and to restore myelination of axons; and as an anti-apoptotic agent or anti-necrotic agent in the central nervous system (all claimed). Also for treating or preventing cell damage or cell death in response to diseases and injury resulting from septic shock, ischemia, ulcers, gastritis, ulcerative colitis, Crohn's disease, diabetes, rheumatoid arthritis, asthma, cirrhosis, allograft rejection, transplant rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis glomerulonephritis, uveitis, glaucoma, blepharitis, chalazion, allergic eye disease, corneal ulcer, keratitis, cataract, retinal disorder, age-related macular degeneration, optic neuritis ileitis, inflammation induced by overproduction of inflammatory cytokines, hemorrhagic shock, anaphylactic shock, burn, infection leading to the overproduction of inflammatory cytokines induced by bacteria, virus, fungus, and parasites, hemodialysis, chronic fatigue syndrome, **cancers**, cardiovascular diseases associated with overproduction of inflammatory cytokines, heart disease,

cardiopulmonary bypass, ischemic/reperfusion injury, ischemic reperfusion associated with overproduction of inflammatory cytokines, toxic shock syndrome, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, dermatitis, urticaria, cerebral ischemia, systemic lupus erythematosis, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, epilepsy, gastrointestinal motility disorders, obesity, hyperphagia, neuroblastoma, malaria, hematologic **cancers**, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, chronic hepatitis C, paraquat poisoning, transplant rejection and preservation, fertility enhancement, bacterial translocation, circulatory shock, traumatic shock, hemodialysis and hangover. The restoration of myelination where depletion due to trauma, toxin exposure, asphyxia or hypoxia-ischemia, perinatal hypoxic-ischemic injury, injury to or disease of the white matter of the CNS, acute brain injury, chronic neurodegenerative disease including multiple sclerosis, demyelinating diseases and disorders including acute disseminated encephalomyelitis, optic neuritis, transverse myelitis; non-inflammatory involvement; progressive multi focal leukoencephalopathy, and central pontine myelinolysis.

ADVANTAGE - (cPG) acts through the mGlu2/3 receptor to bring neuroprotective effect. (cPG) is not only acts as potent neuroprotective agent but also serves as neurogenesis agent. cPG is very stable molecule, so it is administered over extended periods. In regulating IGF-1 induction (cPG) provides neuroprotection with less potential for growth side effects.

Dwg.0/5

L15 ANSWER 6 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2004-106485 [11] WPIDS
DOC. NO. CPI: C2004-043202
TITLE: New bicyclic pyrimidinyl derivatives useful for treating e.g. cognitive disorders, asthma, glaucoma, and Parkinson's disease.
DERWENT CLASS: B03
INVENTOR(S): CASTELHANO, A L; MCKIBBEN, B
PATENT ASSIGNEE(S): (OSIP-N) OSI PHARM INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003139427	A1	20030724	(200411)*		105

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2003139427	A1	US 2002-227378	20020823

PRIORITY APPLN. INFO: US 2002-227378 20020823

AN 2004-106485 [11] WPIDS
AB US2003139427 A UPAB: 20040213
NOVELTY - Bicyclic pyrimidinyl derivatives are new.
DETAILED DESCRIPTION - Bicyclic pyrimidinyl derivatives of formula (I), their salts, prodrugs or active metabolites are new.
Y = N or CR5;
X = N or CR6;
R1 and R2 = alkyl, aryl or alkylaryl (all optionally substituted), H, alkoxy or aminoalkyl;
R1+R2 = optionally substituted heterocyclic ring(s);
R3 and R4 = alkyl, aryl or alkylaryl (all optionally substituted) or H;
R5 and R6 = optionally substituted alkyl, aryl, alkylaryl, amino, H, or halo;
R4+R5 and R5+R6 = optionally substituted heterocyclic or carbocyclic ring.
INDEPENDENT CLAIMS are included for the following:
(1) a composition comprising (I) and a steroid, beta 2-agonist, glucocorticoid, leukotriene antagonist or anticholinergic agonist;
(2) a combination therapy for Parkinson's disease involving (I) and a dopamine enhancer;
(3) a combination therapy for **cancer** involving (I) and a cytotoxic agent;
(4) a combination therapy (M1) for glaucoma involving (I) and a prostaglandin agonist, a muscarinic agonist or a beta 2-antagonist;
(5) a combination therapy (M2) for glaucoma involving (2-(3H-imidazol-4-yl)-ethyl)-(2-phenyl-9H-purin-6-yl)-amine, (2-(3H-imidazol-4-yl)-ethyl)-(6-phenyl-1H-pyrazolo(3,4-d)pyrimidin-4-yl)-amine, (2-(3H-imidazol-4-yl)-ethyl)-(5-phenyl-3H-(1,2,3)triazolo(4,5-d)pyrimidin-7-yl)-amine and at least one of beta -adrenoceptor antagonist, alpha -2 adrenoceptor agonist, carbonic anhydrase inhibitor, cholinergic agonist, prostaglandin and prostaglandin receptor agonist, angiotensin converting enzyme (ACE) inhibitor, **AMPA receptor** antagonist, 5-HT agonist, angiogenesis inhibitor, NMDA antagonist, renin inhibitor, cannabinoid receptor agonist, angiotensin receptor antagonist, hydrochlorothiazide (HCTZ), somatostatin agonist, glucocorticoid antagonist, mast cell degranulation inhibitor, alpha -adrenergic receptor blocker, alpha -2-adrenoceptor antagonist, thromboxane A2 mimetic, protein kinase inhibitor, prostaglandin F derivative, prostaglandin-2 alpha antagonist, dopamine D1 and 5-HT2 agonist, nitric-oxide-releasing agent, 5-HT2 antagonist, cyclooxygenase inhibitor, inosine, dopamine D2 receptor and alpha -2 adrenoceptor agonist, dopamine D1 receptor antagonist and D2 receptor agonist, vasopressin receptor antagonist, endothelin antagonist, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) and related analog and prodrugs, thyroid hormone receptor ligand, muscarinic M1 agonist, sodium channel blocker, mixed action channel blocker, beta adrenoceptor antagonist and PGF2 alpha agonist combination, guanylate cyclase activator, nitrovasodilator, endothelin receptor modulator, actin disrupter, ethacrynic acid, other phenoxyacetic acid analog, calcium channel blockers and neuroprotective agent (preferably beta -adrenoceptor antagonist, alpha -2 adrenoceptor agonist, carbonic anhydrase inhibitor, cholinergic agonist, prostaglandin and prostaglandin receptor agonist); and
(6) a packaged composition for treating disease associated with

an A1, A2a or A3 adenosine receptor comprising a container holding (I), and instructions for using (I) in the treatment.

ACTIVITY - Nootropic; Nephrotropic; Antiarrhythmic; Antiulcer; Antiparkinsonian; Antiasthmatic; Antiallergic; Antiinflammatory; Antipyretic; Antipsoriatic; Dermatological; Gastrointestinal-Gen.; Immunosuppressive; Hypotensive; Cytostatic; Cerebroprotective; Cardiant; Antidiarrheic; Antiarthritic; Antithyroid; Antidiabetic; Neuroprotective; Antianemic; Vasotropic; Antiinfertility; CNS Gen.; Respiratory Gen.; Tranquilizer; Ophthalmological.

MECHANISM OF ACTION - Adenylate cyclase stimulator; A1, A2a- and A3 adenosine receptor inhibitor.

The binding efficiency of N-(2-(6-phenyl-1H-pyrazolo(3,4-d)pyrimidin-4-ylamino)-ethyl)-acetamide (T1) for A2a receptor was evaluated by competition radio-ligand binding assay on membranes from the HEK-293 cells (mammalian tissue culture) stably expressing the human A2a receptors. The membranes were diluted in binding buffer (50 mM Tris-HCl pH 7.4 containing 10 mM MgCl2, 1 mM EDTA, 0.25% BSA, 2 U/ml of adenosine deaminase and 1 protease inhibitor tablet/50 ml) (0.2 mg/ml), and incubated with (3H) CGS-21680 (100 nM) at 25 deg. C for 1 hour in presence of (T1). After incubation ice-cold 50 mM TrisHCl buffer containing 10 mM MgCl2 was added and the assay mixture was filtered. The filter plates were dried and counted in a Topcount. (T1) showed Ki of 49.5 nM.

USE - For treating disease associated with A1, A2a or A3 adenosine receptors in mammals (e.g. human) including cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, bronchoconstriction, neutrophil chemotaxis, reflux condition, ulcerative condition, diseases associated locomotor activity, vasodilation, platelet inhibition and neutrophil superoxide generation, senile dementia and Parkinson's disease, asthma, hypersensitivity, allergic rhinitis, chronic obstructive pulmonary disease, hay **fever**, serum sickness, allergic vasculitis, atopic dermatitis, dermatitis, psoriasis, eczema, idiopathic pulmonary fibrosis, eosinophilic chlorecystitis, chronic airway inflammation, hypereosinophilic syndrome, eosinophilic gastro-enteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, diarrhea, ulcerative colitis, allergic granulomatosis, **carcinomatosis**, eosinophilic granuloma, familial histiocytosis, hypertension, mast cell degranulation, **tumor**, cardiac hypoxia, cerebral ischemia, diuresis, renal failure, neurological disorder, mental disorder, myocardial ischemia, arthritis, autoimmune disease, Crohn's disease, Grave's disease, diabetes, multiple sclerosis, anaemia, fertility disorders, lupus erythematosus, reperfusion injury, brain arteriole diameter, the release of allergic mediators, scleroderma, stroke, global ischemia, central nervous system disorder, cardiovascular disorder, renal disorder, inflammatory disorder, gastrointestinal disorder, eye disorder (e.g. retinal or optic nerve head damage including glaucoma, edema, trauma, hypoxia), allergic disorder, respiratory disorder and immunological disorder. Dwg.0/0

L15 ANSWER 7 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-555960 [52] WPIDS

DOC. NO. CPI: C2003-150088
TITLE: New (2-(3H-imidazol-4-yl)-ethyl)-(2-phenyl-7H-pyrrolo(2,3-d)pyrimidin-4-yl)-amine used as A3 adenosine receptor inhibitor for treating e.g. glaucoma, asthma, hypertension and neurological disorders.
DERWENT CLASS: B02
INVENTOR(S): CASTELHANO, A L; MCKIBBEN, B; WITTER, D J
PATENT ASSIGNEE(S): (CAST-I) CASTELHANO A L; (MCKI-I) MCKIBBEN B; (WITT-I) WITTER D J; (OSIP-N) OSI PHARM INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003073708	A1	20030417	(200352)*		77
US 6673802	B2	20040106	(200411)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2003073708	A1	Provisional	US 2000-250748P	20001201
			US 2001-6405	20011130
US 6673802	B2	Provisional	US 2000-250748P	20001201
			US 2001-6405	20011130

PRIORITY APPLN. INFO: US 2000-250748P 20001201; US 2001-6405 20011130
AN 2003-555960 [52] WPIDS
AB US2003073708 A UPAB: 20030813
NOVELTY - (2-(3H-Imidazol-4-yl)-ethyl)-(2-phenyl-7H-pyrrolo(2,3-d)pyrimidin-4-yl)-amine (I) or its salts are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a combination therapy for glaucoma which comprises (I) and at least one of beta adrenoceptor antagonists, alpha -2 adrenoceptor agonists, carbonic anhydrase inhibitors, cholinergic agonists, prostaglandins and prostaglandin receptor agonists, angiotensin converting enzyme (ACE) inhibitors, **alpha -amino -3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor** antagonists, 5-hydroxytryptamine (5-HT) agonists, angiogenesis inhibitors, N-methyl-D-aspartate antagonists, renin inhibitors, cannabinoid receptor agonists, angiotensin receptor antagonists, hydrochlorothiazide (HCTZ), somatostatin agonists, glucocorticoid antagonists, mast cell degranulation inhibitors, alpha -adrenergic receptor blockers, alpha -2 adrenoceptor antagonists, thromboxane A2 mimetics, protein kinase inhibitors, prostaglandin F derivatives, prostaglandin-2 alpha antagonists, dopamine D1 and 5-HT2 agonists, nitric oxide releasing agents, 5-HT2 antagonists, cyclooxygenase inhibitors, inosine, dopamine D2 receptor and alpha -2 adrenoceptor agonists, dopamine D1 receptor antagonist and D2 receptor agonists, vasopressin receptor antagonists, endothelin antagonists, 1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) or its analogs and

prodrugs, thyroid hormone receptor ligands, muscarinic M1 agonists, sodium channel blockers, mixed action ion channel blockers, beta adrenoceptor antagonist and PGF2 alpha agonist combinations, guanylate cyclase activators, nitrovasodilators, endothelin receptor modulators, ethacrynic acid, other phenoxyacetic acid analogs, actin disrupters, calcium channel blockers and neuroprotective agents; and

(2) a packaged composition comprising a container holding (I), and instructions for using (I).

ACTIVITY - Antiasthmatic; Antipyretic; Antiallergic; Dermatological; Antiinflammatory; Cardiant; Antianginal; Antiulcer; Cytostatic; Nephrotropic; Neuroprotective; Nootropic; Antiarthritic; Immunosuppressive; Antiinfertility; Antithyroid; Antidiabetic; Vasotropic; Cerebroprotective; Hypotensive; Antianemic; Respiratory; Antiarteriosclerotic.

MECHANISM OF ACTION - Adenosine A3 receptor inhibitor.

Tests are described, but no relevant results are given.

USE - Used for treating damage to the eye (e.g. retina or optic nerve head) and glaucoma (all claimed) and also for treating asthma, hypersensitivity, rhinitis, hay **fever**, serum sickness, allergic vasculitis, atopic dermatitis, dermatitis, eczema, idiopathic pulmonary fibrosis, eosinophilic chlorecystitis, chronic airway inflammation, hypereosinophilic syndromes, eosinophilic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, **carcinomatosis**, eosinophilic granuloma, familial histiocytosis, hypertension, mast cell degranulation, **tumor**, cardiac hypoxia, cerebral ischemia, diuresis, renal failure, neurological disorder, mental disorder, cognitive disorder, myocardial ischemia, bronchoconstriction, arthritis, autoimmune disease, Crohn's disease, Grave's disease, diabetes, multiple sclerosis, anemia, psoriasis, fertility disorders, lupus erythematosus, reperfusion injury, brain arteriole diameter, the release of allergic mediators, scleroderma, stroke, global ischemia, central nervous system disorder, cardiovascular disorder, renal disorder, inflammatory disorder, gastrointestinal disorder, eye disorder, allergic disorder, respiratory disorder, immunological disorder, angina, infarction, cerebrovascular ischemia, intermittent claudication, critical limb ischemia, venous hypertension, varicose veins, venous ulceration and arteriosclerosis.

Dwg.0/0

L15 ANSWER 8 OF 33 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2003208634 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12730992
TITLE: Interleukin-1beta promotes oligodendrocyte death through glutamate excitotoxicity.
AUTHOR: Takahashi Jennifer L; Giuliani Fabrizio; Power Christopher; Imai Yoshinori; Yong V Wee
CORPORATE SOURCE: Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada.
SOURCE: Annals of neurology, (2003 May) 53 (5) 588-95. Journal code: 7707449. ISSN: 0364-5134.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

Searcher : Shears 571-272-2528

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030506
Last Updated on STN: 20030605
Entered Medline: 20030604

AB Glutamate excitotoxicity is implicated in the progressive loss of oligodendrocytes in multiple sclerosis, but how glutamate metabolism is dysregulated in the disease remains unclear. Because there is microglia activation in all stages of multiple sclerosis, we determined whether a microglia product, interleukin-1beta, could provide the mechanism for glutamate excitotoxicity. We found that whereas interleukin-1beta did not kill oligodendrocytes in pure culture, it produced apoptosis of oligodendrocytes in coculture with astrocytes and microglia. This requirement for a mixed glia environment suggests that interleukin-1beta impairs the well-described glutamate-buffering capacity of astrocytes. In support, antagonists at **AMPA**/kainate glutamate **receptors**, NBQX and CNQX, blocked the interleukin-1beta toxicity to oligodendrocytes. Another microglia/macrophage cytokine, **tumor** necrosis factor-alpha, also evoked apoptosis of oligodendrocytes in a mixed glia environment in an NBQX-blockable manner. These results provide a mechanistic link between the persistent and insidious microglia activation that is evident in all stages of multiple sclerosis, with the recent appreciation that glutamate excitotoxicity leads to the destruction of oligodendrocytes in the disease.

L15 ANSWER 9 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003421962 EMBASE
TITLE: The relevance of alternative RNA splicing to pharmacogenomics.
AUTHOR: Bracco L.; Kearsey J.
CORPORATE SOURCE: L. Bracco, ExonHit Therapeutics, 65 Bd Massena, 75013 Paris, France. laurent.bracco@exonhit.com
SOURCE: Trends in Biotechnology, (2003) 21/8 (346-353).
Refs: 87
ISSN: 0167-7799 CODEN: TRBIDM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The importance of alternative RNA splicing in the generation of genetic diversity is now widely accepted. This article highlights how alternative RNA splicing can have an impact on drug efficacy and safety, and demonstrates its potential pharmacogenomic value. The analysis of the repertoire of alternative RNA splicing events could potentially identify markers of pharmacogenomic relevance with high sensitivity and specificity and also provides a route through which genes can be selected for single nucleotide polymorphism (SNP) genotyping. Recent methodological advances, including microarray and

splice-dedicated expression profiling, have made it possible to perform high-throughput alternative splicing analyses.

L15 ANSWER 10 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003170405 EMBASE
TITLE: Pharmacologic manipulation of the labyrinth with novel and traditional agents delivered to the inner ear.
AUTHOR: Seidman M.D.; Van De Water T.R.
CORPORATE SOURCE: Dr. M.D. Seidman, Department of Otologic Surgery, Henry Ford Medical Center, 6777 W. Maple Rd., West Bloomfield, MI 48322, United States. mseidma1@hfhs.org
SOURCE: Ear, Nose and Throat Journal, (1 Apr 2003) 82/4 (276-300).
Refs: 207
ISSN: 0145-5613 CODEN: ENTJDO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We describe the methodology and rationale behind the delivery of therapeutic medicines to the inner ear. The inner ear has long been impervious to pharmacologic manipulation. This is most likely the result of a protective mechanism called the blood-labyrinth barrier, whose function closely resembles that of the blood-brain barrier. This protective barrier impedes the clinician's ability to treat inner ear diseases with systemically administered medications. Since 1935, otolaryngologists have attempted to manipulate the inner ear with transtympanically injected medicines. Success has varied widely, but medicinal ablation of vestibular function can be achieved in this manner. Unfortunately, the auditory system is also at great risk from any medicine that is delivered to the inner ear via the middle ear. Over the past 10 years, significant improvements in drug delivery have allowed for more "titratable" treatment, which has reduced (but not eliminated) the risk of permanent hearing loss. In this article, we discuss both novel and time-tested methods of delivering medicines to the inner ear. We also review the classes of medications that alter inner ear function and the attendant risks of such treatments.

L15 ANSWER 11 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2002-636520 [68] WPIDS
CROSS REFERENCE: 2002-479191 [51]; 2002-690393 [74]; 2003-380676 [36]
DOC. NO. CPI: C2004-013555
TITLE: New N-6 substituted 7-deazapurine compounds useful for treating e.g. disease associated with adenosine receptor.
DERWENT CLASS: B02
INVENTOR(S): CASTELHANO, A L; MCKIBBEN, B; WITTER, D J

PATENT ASSIGNEE(S): (OSIP-N) OSI PHARM INC
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002057267	A1	20020725	(200268)*	EN	320
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZM ZW					
NO 2003002482	A	20030728	(200361)		
EP 1347980	A1	20031001	(200365)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
KR 2003051890	A	20030625	(200373)		
US 6664252	B2	20031216	(200382)		
US 6680322	B2	20040120	(200407)		
BR 2001015847	A	20040225	(200416)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2002057267	A1		WO 2001-US45280	20011130
NO 2003002482	A		WO 2001-US45280	20011130
			NO 2003-2482	20030602
EP 1347980	A1		EP 2001-997029	20011130
			WO 2001-US45280	20011130
KR 2003051890	A		KR 2003-707247	20030529
US 6664252	B2	Provisional	US 1999-169037P	19991202
			US 2000-728607	20001201
US 6680322	B2	Provisional	US 1999-168803P	19991202
			US 2000-728316	20001201
BR 2001015847	A		BR 2001-15847	20011130
			WO 2001-US45280	20011130

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1347980	A1	Based on	WO 2002057267
BR 2001015847	A	Based on	WO 2002057267

PRIORITY APPLN. INFO: US 2000-728616 20001201; US 2000-728316 20001201; US 2000-728607 20001201; US 1999-169037P 19991202; US 1999-168803P 19991202

AN 2002-636520 [68] WPIDS

CR 2002-479191 [51]; 2002-690393 [74]; 2003-380676 [36]

AB WO 200257267 A UPAB: 20040305

NOVELTY - N-6 substituted 7-deazapurine compounds or their salts are new.

DETAILED DESCRIPTION - N-6 substituted 7-deazapurine compounds

of formula (I), (II), (III) or their salts are new.

R1NR2 = 2-carboxamido-1-pyrolidinyl or 2-carboxamido-4-hydroxy-1-pyrolidinyl;

R1 = H;

R2 = hydroxycyclohexyl;

R5 = H, optionally substituted alkyl or alkylaryl.

INDEPENDENT CLAIMS are included for the following:

(1) A water soluble prodrug of (I), (II) and (III) which is metabolized in vivo to produce an active drug which selectively inhibits A1 adenosine receptor;

(2) Inhibiting the activity of A1 adenosine receptor in a cell involving contacting the cell (preferably human cell) with (I);

(3) A combination therapy for asthma involving (I), and a steroid, beta agonist-2, glucocorticoid, lucotriene antagonist or anticolinergic agonist;

(4) A pharmaceutical composition comprising (I), (II) or (III) and a carrier;

(5) A packaged pharmaceutical composition comprising a container holding (I), (II), (III) or (IV) and instructions for using them;

(6) A contamination therapy for Parkinson's disease involving (II) or (III) and any of the dopamine enhancers;

(7) A combinational therapy for **cancer** involving (II) or (III) and any of the cytotoxic agents;

(8) A combinational therapy for glaucoma involving (II) or (III) and a prostaglandin agonist, a muscarinic agonist or a beta antagonist-2; and

(9) Inhibiting the activity of A3 adenosine receptor in a cell involving contacting the cell with (IV).

ACTIVITY - Nootropic; Cardiant; Antiinflammatory; Antiulcer; Antiasthmatic; Antiallergic; Antiparkinsonian; Ophthalmological; Cytostatic; Dermatological; Vasotropic; Antirheumatic; Antiarthritic; Osteopathic; Antipyretic; Antiemetic; Antidiarrheic; Antiarrhythmic; Anorectic; Hypotensive; Antipsoriatic; Immunosuppressive; Antithyroid; Antidiabetic; Antianemic; Antiinfertility. I

MECHANISM OF ACTION - Adenosine receptor antagonist-2A; Adenosine receptor antagonist-A2A; Adenosine receptor antagonist-3A.

USE - For treating disease associated with A1 adenosine receptor in a subject (preferably mammal, especially human) including cognitive disease, renal failure, cardiac arrhythmias, respiratory epithelia, transmitter release, sedation, vasoconstriction, bradycardia, negative cardiac inotropy and dromotropy, bronchoconstriction, nentropil chemotaxis, reflux condition or ulcerative condition, asthma, chronic obstructive pulmonary disease, allergic rhinitis or an upper respiratory disorder, heart failure, A2a adenosine receptor including locomotor activity, vasodilation, platelet inhibition, neutrophil superoxide generation, cognitive disorder, senile dementia or parkinson's disease by stimulating adenylate cyclase; treating damage of the eye including retinal or optic nerve head damage, glaucoma, **cancer** (all claimed). Also used for treating bronchitis, gastrointestinal disorder, edema, ischemia, hypoxia or trauma, release of toxins inflammation, coma, water retention, weight gain or weight loss, pancreatitis, emphysema, rheumatoid arthritis, osteoarthritis, multiple organ failure, infant and adult respiratory

distress syndrome, skin **tumor** promotion, immunodeficiency, **fever**, shortness of breath, nausea, diarrhea, weakness, headache, CNS effects, cardiovascular effects, renal effects, respiratory effects, immunological effects, gastro-intestinal effects, metabolic effects, Alzheimer's disease, memory enhancement, arrhythmia, tachycardia, angiogenesis, obesity and hypertension, hay **fever**, serum sickness, allergic vasculitis, atopic dermantitis, dermantitis, psoriasis, idiopathic pulmonary fibrosis, eosinophillic chlorecystitis, chronic airway inflammation, hyperesosinphilic syndromes, eosinophilic gastroenteritis, edema, urticaria, eosinophilic myocardial disease, episodic angioedema with eosinophilia, inflammatory bowel disease, ulcerative colitis, allergic granulomatosis, **carcinomatosis**, eosinophilic granuloma, familial histiocytosis, mast cell degranulation, **tumor**, cardiac hypoxia, cerebral ischemia, diuresis, neurological disorder, cognitive disorder, myocardial ischemia, bronchoconstriction, arthritis, Crohn's disease, Grave's disease, diabetes, multiple sclerosis, anaemia, fertility disorder, lupus erythyematosus, reperfusion injury, brain arteriole diameter, the release of allergic mediators, scleroderma, global ischemia.

ADVANTAGE - The compounds eliminate or inhibit growth of pathogens and are selectively toxic to the pathogen while producing minimal or no deleterious effects upon the infected host subject.

Dwg.0/0

L15 ANSWER 12 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2002-599681 [64] WPIDS

DOC. NO. CPI: C2002-169502

TITLE: New substituted felbamate derivatives useful in the treatment of neurological disease e.g. epileptic seizures.

DERWENT CLASS: B03 B05

INVENTOR(S): MACDONALD, T L

PATENT ASSIGNEE(S): (UYVI-N) UNIV VIRGINIA PATENT FOUND; (MACD-I) MACDONALD T L

COUNTRY COUNT: 97

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002056827	A2	20020725	(200264)*	EN	43

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

EP 1337218 A2 20030827 (200357) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

US 2004023986 A1 20040205 (200411)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2002056827 A2	WO 2001-US47665	20011023
EP 1337218 A2	EP 2001-994186	20011023
	WO 2001-US47665	20011023
US 2004023986 A1	WO 2001-US47665	20011023
	US 2003-415167	20030425

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1337218	A2	Based on	WO 2002056827

PRIORITY APPLN. INFO: US 2000-243024P 20001025; US 2000-243023P 20001025; US 2003-415167 20030425

AN 2002-599681 [64] WPIDS

AB WO 200256827 A UPAB: 20021007

NOVELTY - Substituted felbamate derivatives (I) and (I') are new.

DETAILED DESCRIPTION - Substituted felbamate derivatives of formula (I) and (I') are new.

R2 = F or Cl;

R3 = OH or -OCONH2;

R1 = 1-9C alkyl, 3-9C cycloalkyl (optionally **alkylated** with 1-9C alkyl), or a group of formula (i) - (iv);

A' and B' = CH or N;

R7 = H, halo, alkyl, haloalkyl or OH;

X = -O-, -N- or -S-;

m = 0 - 3;

n = 1 - 3;

R8 and R9 = H, halo, OH or (halo)alkyl;

R'1 = a group of formula (v) or T;

T = 3-9C cycloalkyl, 2-thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-(1,3-diazinyl), 4-(1,3-diazinyl), 5-(1,3-diazinyl), 2-(1,4-diazinyl), 2-imidazolyl, 4-imidazolyl, 2-(1,3-oxazinyl), 4-(1,3-oxazinyl), 5-(1,3-oxazinyl), or 2-, 4- or 5-thiazinyl; and provided only one of A' and B' is N.

An INDEPENDENT CLAIM is included for a pharmaceutical composition containing a compound of formula (II).

R''1 = 1-9C alkyl, 1-9C **alkylated** 3-9C cycloalkyl, -(CH2)n-Ph or T.

ACTIVITY - Analgesic; Neuroleptic; Ophthalmological; Anticonvulsant; Antidepressant; Vasotropic; Cerebroprotective; Cardiant; Nootropic; Neuroprotective; Anti-HIV; Anorectic; Antidiabetic; Tranquilizer; Vulnerary; Antibacterial; Immunosuppressive; Neuroleptic; Antiaddictive; Antiinflammatory; Hepatotropic; Antidote.

Test details are described but no results given.

MECHANISM OF ACTION - N-methyl-D-aspartate (NMDA) **receptor** modulator; **AMPA**/kainate **receptor** modulator; Na.sup.+channel conductance modulator; Delayed neuronal cell death due to kainic acid induced status epilepticus inhibitor; Presynaptic inhibition by GABA inducer; Glycine-site strychnine insensitive antagonist; D2 (Dopamine receptor) antagonist.

USE - (I) and (I') are useful for treating a patient suffering from neuropathic pain, neurologic disorder, tissue damage resulting from localized hypoxic conditions and glaucoma, (all claimed); such

as for treating epileptic seizures, acute and chronic neurodegenerative conditions, cellular damage caused by myocardial or cerebral ischemia, reperfusion injuries resulting from stroke, spinal-chord perfusion type injuries, diabetic neuropathy, peripheral neuropathy, terminal **cancer** pain, failed back injury, chronic pain. The neurologic disorders include spasticity (both supraspinal and spinal lesions), and neurologic and disorders that involve excessive activation of the N-methyl-D-aspartate (NMDA) receptor such as sepsis, meningitis, central nervous system vasculitis, adrenoleukodystrophy, impotence, schizophrenia, drug addiction, fatigue (including fatigue associated with chronic diseases, such as e.g. multiple sclerosis, post-polio syndrome, Parkinson's disease and chronic fatigue syndrome), lead poisoning, mitochondrial myopathies, childbirth complications (such as e.g. premature labor, prolonged labor, hypoxia, which place the fetus at risk for cerebral ischemic damage and cerebral palsy), surgical anesthesia (e.g. as a prophylactic treatment to reduce risk of brain damage from hypoxia, anoxia, cerebral embolism (e.g. fat or air), hypotension or hypoglycemia), traumatic head and spinal cord injury, hypoglycemia, Tourette's syndrome, hepatic encephalopathy, obesity, diabetes, other genetic obesity disorders). Also useful for treating neuropsychiatric disorders (including depression including primary depression, or secondary depression due to systemic diseases including infections, endocrine disorders, collagen vascular diseases, nutritional deficiencies and **neoplastic** diseases and neurological diseases (including head trauma, cerebral **tumors**, post-stroke early dementing illness, and sleep apnea) occurring in e.g. post-myocardial infarct patients; and mood disorders, attention deficit disorders); and acute and chronic neurodegenerative conditions (including Alzheimer's disease, HIV dementia, amyotrophic lateral sclerosis, spinal cord injury, narcolepsy).

ADVANTAGE - The compounds exhibit therapeutic properties similar to those of the prior art felbamate derivatives without producing the adverse reactions or side effects associated with the prior art derivatives by avoiding the formation of the toxic metabolite atropaldehyde.

Dwg.0/0

L15 ANSWER 13 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-018588 [01] WPIDS
CROSS REFERENCE: 2001-541358 [60]; 2003-532533 [50]
DOC. NO. NON-CPI: N2003-014435
DOC. NO. CPI: C2003-004377
TITLE: Validating the therapeutic or pharmacological potential of target molecules e.g. receptors by using a genetically modified animal which expresses a silent metal-ion site in a potential drug target.
DERWENT CLASS: A96 B04 B05 D16 S03
INVENTOR(S): LANGE, B H; RIST, O; SCHWARTZ, T W
PATENT ASSIGNEE(S): (SEVE-N) 7TM PHARMA AS
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2002054077 A2 20020711 (200301)* EN 78
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002054077 A2		WO 2001-DK867	20011221

PRIORITY APPLN. INFO: US 2001-280237P 20010330; WO 2000-EP13389 20001229; DK 2001-536 20010330

AN 2003-018588 [01] WPIDS
CR 2001-541358 [60]; 2003-532533 [50]
AB WO 200254077 A UPAB: 20030805

NOVELTY - Target validation process for testing or validating physiological importance, therapeutic of biological target molecule (TM), involves introducing silent metal ion site (SMIS) in TM to obtain an engineered TM, testing a compound for its ability to bind to the SMIS in the TM, testing the compound in a genetically modified test animal with the engineered TM and monitoring certain parameters of the animal.

DETAILED DESCRIPTION - A target validation process for testing or validating physiological importance, therapeutic of a biological target molecule (TM), involves introducing a silent metal ion site (SMIS) in TM to obtain an engineered TM, testing a compound for its ability to bind to the SMIS in the TM, testing the compound in a genetically modified test animal with the engineered TM and monitoring certain parameters of the animal. The method comprises:

(i) introduction of a silent metal ion site in TM to obtain a silent metal ion engineered TM;

in vitro testing of a test compound for its ability to bind to the introduced silent metal ion site in the silent metal ion engineered TM;

(ii) optionally, chemically optimizing the test compound and/or the biological TM to create secondary interaction(s) with chemical groups in the vicinity of the metal ion site in the silent metal ion engineered TM;

(iii) optionally, repeating ii) and iii) and to obtain a suitable binding affinity in the in vitro test;

(iv) optionally, chemically optimizing the test compound to improve the pharmacokinetic and/or biopharmaceutical properties of the test compound;

(v) preparing a genetically modified test animal containing the silent metal ion site engineered TM; and

in vivo testing of the optionally optimized test compound in the genetically modified test animal, and monitoring the biochemical, physiological and/or behavior parameters of the test animal.

USE - The method is useful for target validation process for

testing or validating physiological importance and/or therapeutic of a biological TM such as proteins, polypeptides, oligopeptides, nucleic acids, carbohydrates, nucleoproteins, glycoproteins, glycolipids, lipoproteins and their derivatives, membrane receptors, signal transduction proteins, scaffolding proteins, nuclear receptors, steroid receptors, intracellular receptors, transcription factors, enzymes, allosteric enzyme regulator proteins, growth factors, hormones, neuropeptides or immunoglobulins.
Dwg.0/5

L15 ANSWER 14 OF 33 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002664054 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12424735
TITLE: The DNA damaging agent **etoposide** activates a cell survival pathway involving alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors and mitogen-activated protein kinases in hippocampal neurons.
AUTHOR: Lu Chengbiao; Fu Weiming; Zhao Daohong; Mattson Mark P
CORPORATE SOURCE: Laboratory of Neurosciences, National Institute on Aging/NIH, 5600 Nathan Shock Drive, Baltimore, MD 21224, USA.
SOURCE: Journal of neuroscience research, (2002 Dec 1) 70 (5) 671-9.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021109
Last Updated on STN: 20030124
Entered Medline: 20030123

AB **Etoposide**, an inhibitor of topoisomerase II that induces DNA damage and can trigger cell death, is used as a chemotherapeutic agent. Because chemotherapies can result in neurological complications and because DNA damage in neurons is implicated in the pathogenesis of several neurodegenerative disorders, we studied the effects of **etoposide** on cultured hippocampal neurons. We found that **etoposide** induces neuronal apoptosis and that, prior to the cell death commitment point, there is an increase in whole-cell alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-induced current but no change in N-methyl-D-aspartate (NMDA)-induced current. Associated with the increase in AMPA-induced current was an increase in the amounts of **AMPA receptor** subunits GluR1 and GluR4, whereas levels of the NMDA receptor subunit NR1 were unaffected by **etoposide**. **AMPA receptor** activation can result in excitotoxic cell death but can also activate signaling pathways that promote synaptic plasticity and cell survival. We found that **etoposide** increases the activation of p42 and p44 mitogen-activated protein (MAP) kinases, and that activation of the MAP kinases by **etoposide** requires **AMPA receptor** activation. Pharmacological blockade of **AMPA receptors** and p42/p44 MAP kinases, but not of

NMDA receptors, exacerbated **etoposide**-induced cell death. These findings suggest that, although **etoposide** is neurotoxic, it also activates a cell survival pathway involving **AMPA receptor**-mediated activation of p42/p44 MAP kinases. Agents that selectively inhibit the cell life or death pathways triggered by DNA damage may prove useful in the settings of **cancer** and neurodegenerative disorders, respectively. Published 2002 Wiley-Liss, Inc.

L15 ANSWER 15 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2002:473662 BIOSIS
DOCUMENT NUMBER: PREV200200473662
TITLE: Effects of systemic and CNS pro-inflammatory cytokines on NMDA and **AMPA receptors**-mediated brain lesions in newborn mice.
AUTHOR(S): Plaisant, Frank [Reprint author]; Dommergues, Marie-Aliette; Campbell, Iain L.; Gressens, Pierre
CORPORATE SOURCE: INSERM E 9935, Hop Robert-Debre, Paris, France
SOURCE: Pediatric Research, (April, 2002) Vol. 51, No. 4 Part 2, pp. 442A. print.
Meeting Info.: Annual Meeting of the Pediatric Societies'. Baltimore, MD, USA. May 04-07, 2002.
CODEN: PEREBL. ISSN: 0031-3998.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Sep 2002
Last Updated on STN: 11 Sep 2002

L15 ANSWER 16 OF 33 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2002111471 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11835309
TITLE: Varied actions of proinflammatory cytokines on excitotoxic cell death in the rat central nervous system.
AUTHOR: Allan Stuart M
CORPORATE SOURCE: School of Biological Sciences, 1.124 Stopford Building, University of Manchester, Oxford Road, Manchester, M13 9PT, United Kingdom.. stuart.allen@man.ac.uk
SOURCE: Journal of neuroscience research, (2002 Feb 15) 67 (4) 428-34.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020215
Last Updated on STN: 20020321
Entered Medline: 20020320

AB Interleukin (IL)-1beta mediates diverse forms of neurodegeneration and exacerbates cell death induced by striatal injection of the excitotoxin alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic

acid (AMPA) in the rat brain. The objective of this study was to determine whether this effect was specific to IL-1beta. Injection of IL-1alpha and AMPA in the striatum had effects identical to those of IL-1beta, whereas coinjection of **IL-6** or **tumor** necrosis factor (TNF)-alpha with AMPA failed to induce significant cortical cell death. In contrast to IL-1alpha, IL-1beta, and **IL-6**, TNFalpha significantly reduced (by 38%) the local striatal damage. These findings suggest that the effect of **IL-1** on **AMPA** **receptor**-mediated cell death in the rat striatum is not mimicked by other proinflammatory cytokines. Furthermore, TNFalpha shows neuroprotective effects against acute excitotoxic injury. Copyright 2002 Wiley-Liss, Inc.

L15 ANSWER 17 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002362996 EMBASE
TITLE: Optimum pharmacologic management of an acute spinal cord injury in the setting of a lumbar burst fracture.
AUTHOR: Chu G.K.T.; Fehlings M.G.
CORPORATE SOURCE: Dr. G.K.T. Chu, Division of Neurosurgery, Toronto Western Hospital, University of Toronto, Toronto, Ont., Canada
SOURCE: Topics in Spinal Cord Injury Rehabilitation, (2002) 8/2 (9-20).
Refs: 83
ISSN: 1082-0744 CODEN: TSIRFP
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Spinal cord injury is a devastating disease that has eluded successful treatment. It has been a long-held belief that most injuries are untreatable. This view is changing as new discoveries are made into the molecular mechanisms of injury and regeneration. This insight has led to the pursuit of new avenues of pharmacotherapy. Although surgical treatment varies with injuries at different levels, pharmacologic management for a lumbar spine burst fracture with spinal cord injury is no different than injuries at other levels. This review will describe some of the inroads made into spinal cord injury and discuss what treatments are now available and what may be in store for the future.

L15 ANSWER 18 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2001-375023 [39] WPIDS
DOC. NO. CPI: C2001-114678
TITLE: Treating central nervous system ischemic or hemorrhagic injury using anti alpha4 integrin antagonists.
DERWENT CLASS: B04 B05 D16
INVENTOR(S): ADAMS, S; LOBB, R; RELTON, J; WHALLEY, E; ADAMS, S

P
PATENT ASSIGNEE(S): (BIOJ) BIOGEN INC; (ADAM-I) ADAMS S P; (LOBB-I) LOBB R; (RELT-I) RELTON J; (WHAL-I) WHALLEY E
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001043774	A1	20010621	(200139)*	EN	41
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001021020	A	20010625	(200162)		
EP 1242118	A1	20020925	(200271)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2002197233	A1	20021226	(200304)		
JP 2003517023	W	20030520	(200334)		63

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001043774	A1		WO 2000-US33942	20001214
AU 2001021020	A		AU 2001-21020	20001214
EP 1242118	A1		EP 2000-984395	20001214
			WO 2000-US33942	20001214
US 2002197233	A1	Provisional	US 1999-171265P	19991216
		Cont of	WO 2000-US33942	20001214
			US 2002-170841	20020613
JP 2003517023	W		WO 2000-US33942	20001214
			JP 2001-544910	20001214

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001021020	A	Based on	WO 2001043774
EP 1242118	A1	Based on	WO 2001043774
JP 2003517023	W	Based on	WO 2001043774

PRIORITY APPLN. INFO: US 1999-171265P 19991216; US 2002-170841 20020613
AN 2001-375023 [39] WPIDS
AB WO 200143774 A UPAB: 20010716
NOVELTY - Treatment (M1) of a central nervous system injury, comprising administration of an alpha 4 integrin antagonist.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for treatment (M2) of a secondary central nervous system injury resulting from an ischemic insult, comprising administration of an alpha 4 integrin antagonist.
ACTIVITY - Vasotropic; hemostatic.

MECHANISM OF ACTION - alpha 4 integrin antagonist.

Groups of male Sprague Dawley (SD) or spontaneously hypertensive rats (SHRs) were treated with either vehicle (PBS) or the bradykinin B2 receptor antagonist Hoe (Hoechst) by continuous subcutaneous infusion via osmotic mini-pumps. Primed mini osmotic pumps (Alza Corp.) were implanted into the subcutaneous space at the scruff of the neck immediately prior to induction of cerebral ischemia. The pumps were loaded to release 300 ng/kg/min Hoe 140 and delivered compound or vehicle at a rate of 8 micro l/hour.

Treatment with the bradykinin B2 receptor antagonist Hoe 140 significantly reduced total, cortical and subcritical infarct volume, by 37%, 43% and 17% respectively, compared to vehicle treated controls measured 24 hours after induction of cerebral ischemia in SHRs. In SD rats treatment with the same dose of Hoe 140 reduced total, cortical and subcritical infarct volume, by 57%, by 93% and 24% respectively, compared to vehicle treated controls (n=7) measured 24 hours after the induction of cerebral ischemia. These data are consistent with previous findings (Relton et. al, 1997 Stroke 28:1430) and were undertaken as a positive control.

In SHRs pretreated with the anti alpha 4 antibody, TA-2 (2.5 mg/kg iv), 24 hours prior to induction of cerebral ischemia significantly reduced total, cortical and subcortical infarct volumes, by 43%, 47% and 33% respectively, compared to animals treated with the same dose of an isotype control antibody measured 24 hours after induction of cerebral ischemia. In SD rats using the same protocol, total, cortical and subcortical infarct volume was significantly reduced by 64%, 65% and 38% respectively. The results show pretreatment with TA-2 antibody provides protection against brain damage in both strains of rats

USE - M1 and M2, are useful for treating central nervous system injury, particularly stroke, traumatic brain injury or spinal cord injury. The injury may be ischemic or hemorrhagic.

Dwg.0/4

L15 ANSWER 19 OF 33 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER:	2001292185 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 11331750
TITLE:	Glutamate antagonists limit **tumor** growth.
COMMENT:	Comment in: Proc Natl Acad Sci U S A. 2001 May 22;98(11):5947-8. PubMed ID: 11371628 Erratum in: Proc Natl Acad Sci U S A 2001 Jul 17;98(15):8921
AUTHOR:	Rzeski W; Turski L; Ikonomidou C
CORPORATE SOURCE:	Department of Pediatric Neurology, Children's Hospital, Charite-Virchow Campus, Humboldt University, Augustenburger Platz 1, D-13353 Berlin, Germany.
SOURCE:	Proceedings of the National Academy of Sciences of the United States of America, (2001 May 22) 98 (11) 6372-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:	English
FILE SEGMENT:	Priority Journals
ENTRY MONTH:	200107

Searcher : Shears 571-272-2528

ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20030105
Entered Medline: 20010719

AB Neuronal progenitors and **tumor** cells possess propensity to proliferate and to migrate. Glutamate regulates proliferation and migration of neurons during development, but it is not known whether it influences proliferation and migration of **tumor** cells. We demonstrate that glutamate antagonists inhibit proliferation of human **tumor** cells. Colon adenocarcinoma, astrocytoma, and breast and lung **carcinoma** cells were most sensitive to the antiproliferative effect of the N-methyl-d-aspartate antagonist dizocilpine, whereas breast and lung **carcinoma**, colon adenocarcinoma, and neuroblastoma cells responded most favorably to the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate antagonist GYKI52466. The antiproliferative effect of glutamate antagonists was Ca(2+) dependent and resulted from decreased cell division and increased cell death. Morphological alterations induced by glutamate antagonists in **tumor** cells consisted of reduced membrane ruffling and pseudopodial protrusions. Furthermore, glutamate antagonists decreased motility and invasive growth of **tumor** cells. These findings suggest **anticancer** potential of glutamate antagonists.

L15 ANSWER 20 OF 33 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001669097 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11714908
TITLE: Insights into the mechanisms of ifosfamide encephalopathy: drug metabolites have agonistic effects on **alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic** acid (**AMPA**)/kainate **receptors** and induce cellular acidification in mouse cortical neurons.
AUTHOR: Chatton J Y; Idle J R; Vagbo C B; Magistretti P J
CORPORATE SOURCE: Institute of Physiology and Laboratory of Neurological Research, Department of Neurology, University of Lausanne Medical School, Lausanne, Switzerland.. jean-yves.chatton@iphysiol.unil.ch
SOURCE: Journal of pharmacology and experimental therapeutics, (2001 Dec) 299 (3) 1161-8. Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011121
Last Updated on STN: 20020123
Entered Medline: 20011220

AB Therapeutic value of the **alkylating** agent ifosfamide has been limited by major side effects including encephalopathy. Although the underlying biochemical processes of the neurotoxic side effects are still unclear, they could be attributed to metabolites rather than to ifosfamide itself. In the present study, the effects of selected ifosfamide metabolites on indices of neuronal activity have been investigated, in particular for S-carboxymethylcysteine

(SCMC) and thiodiglycolic acid (TDGA). Because of structural similarities of SCMC with glutamate, the Ca(2+)(i) response of single mouse cortical neurons to SCMC and TDGA was investigated. SCMC, but not TDGA, evoked a robust increase in Ca(2+)(i) concentration that could be abolished by the **alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic** acid (**AMPA**)/kainate **receptor** antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), but only partly diminished by the N-methyl-D-aspartate receptor antagonist 10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK=801). Cyclothiazide (CYZ), used to prevent **AMPA**/kainate **receptor** desensitization, potentiated the response to SCMC. Because activation of **AMPA**/kainate **receptors** is known to induce proton influx, the intracellular pH (pH(i)) response to SCMC was investigated. SCMC caused a concentration-dependent acidification that was amplified by CYZ. Since H(+)/monocarboxylate transporter (MCT) activity leads to similar cellular acidification, we tested its potential involvement in the pH(i) response. Application of the lactate transport inhibitor quercetin diminished the pH(i) response to SCMC and TDGA by 43 and 51%, respectively, indicating that these compounds may be substrates of MCTs. Taken together, this study indicates that hitherto apparently inert ifosfamide metabolites, in particular SCMC, activate **AMPA**/kainate **receptors** and induce cellular acidification. Both processes could provide the biochemical basis of the observed ifosfamide-associated encephalopathy.

L15 ANSWER 21 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:509440 BIOSIS
DOCUMENT NUMBER: PREV200100509440
TITLE: **Interferon**-gamma potentiates neuronal sensitivity to ischemia and glutamate neurotoxicity.
AUTHOR(S): Lambersten, K. L. [Reprint author]; Gregersen, R. [Reprint author]; Frandsen, A.; Owens, T.; Finsen, B. [Reprint author]
CORPORATE SOURCE: Anatomy and Neurobiology, University of Southern Denmark, Odense University, Odense, Denmark
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 877. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Oct 2001
Last Updated on STN: 23 Feb 2002

AB Presence of the lymphocyte-derived cytokine **interferon**-gamma (**IFNgamma**) within the CNS is usually a predictor of pathology. Using a murine model of focal cerebral ischemia, we found that mice deficient in **IFNgamma** or **IFNgamma** receptors and wildtype mice developed similarly sized neocortical infarcts. In comparison, transgenic mice with myelin basic protein

(MBP) promoter-driven expression of **IFNgamma** in their CNS developed significantly larger infarcts than non-transgenic mice both 1 and 5 days after middle cerebral artery occlusion. **IFNgamma**-transgenic mice showed increased accumulation of **tumor** necrosis factor (TNF) synthesizing Mac-1+ microglia-macrophages in peri-infarct areas and white matter by day 5, corresponding to areas with elevated MBP gene transcription. However, findings of comparable numbers of TNF mRNA-expressing microglia-macrophages in **IFNgamma**-transgenic and non-transgenic mice at day 1 suggested that the increased infarction could not be attributed to TNF alone. Consistent with these data, **IFNgamma** enhanced the sensitivity of primary neocortical murine neurons to **AMPA** and NMDA **receptor** -stimulation. Our findings indicate that the increased infarct size in **IFNgamma**-transgenic mice can be attributed to a direct effect of **IFNgamma** sensitizing the neocortical neurons to glutamate receptor-stimulation. This direct effect of **IFNgamma** on CNS neurons may contribute to other CNS-pathologies such as multiple sclerosis.

L15 ANSWER 22 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002209052 EMBASE
TITLE: Recent advances in pain research: Implications for chronic headache.
AUTHOR: Jensen T.S.
CORPORATE SOURCE: T.S. Jensen, Department of Neurology, Danish Pain Research Center, Aarhus University Hospital, 8000 Aarhus C, Denmark. tsj@akhphd.au.dk
SOURCE: Cephalalgia, (2001) 21/7 (765-769).
Refs: 40
ISSN: 0333-1024 CODEN: CEPHDF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 008 Neurology and Neurosurgery
017 Public Health, Social Medicine and Epidemiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Within the last 2 decades there has been an explosion in new information on mechanisms underlying pain. Unfortunately this information has not resulted in a similar improvement of our handling of patients with chronic pain including chronic musculoskeletal pain. Neuronal hyperexcitability, which apparently is a key phenomenon in many (if not all) types of chronic pain results in changes in the nervous system from the level of the peripheral nociceptor to the highest cortical centers in the brain. The neuronal plastic changes in chronic pain conditions makes the nociceptive system amenable for treatment with several traditional as well as untraditional types of interventions. Two treatment areas that seem worth exploring within chronic pain including headache concerns preventive measures and endogenous pain modulation.

L15 ANSWER 23 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001442339 EMBASE

TITLE: **Purines** in Portugal.
AUTHOR: Stone T.W.; Zimmermann H.; Lopes L.V.; Schaddelee M.P.
CORPORATE SOURCE: T.W. Stone, Inst. of Biomedical/Life Sciences, University of Glasgow, Glasgow, United Kingdom. T.W.Stone@bio.gla.ac.uk
SOURCE: Trends in Neurosciences, (1 Nov 2001) 24/11 (629-630).
ISSN: 0166-2236 CODEN: TNSCDR
PUBLISHER IDENT.: S 0166-2236(00)01992-5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 24 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2001267400 EMBASE
TITLE: Multiple sclerosis: More than inflammation and demyelination.
AUTHOR: Rieckmann P.; Smith K.J.
CORPORATE SOURCE: K.J. Smith, Dept. of Neuroimmunology, Neuroinflammation Research Group, Guy's, King's/St. Thomas' Sch. Med., London SE1 9RT, United Kingdom. kenneth.smith@kcl.ac.uk
SOURCE: Trends in Neurosciences, (1 Aug 2001) 24/8 (435-437).
Refs: 5
ISSN: 0166-2236 CODEN: TNSCDR
PUBLISHER IDENT.: S 0166-2236(00)01860-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 25 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002454822 EMBASE
TITLE: Glial diffusion barriers during aging and pathological states.
AUTHOR: Sykova E.
CORPORATE SOURCE: E. Sykova, Department of Neuroscience, Institute of Experimental Medicine, Acad. of Sci. of the Czech Republic, Videnska 1083, 142 20 Prague 4, Czech Republic. sykova@biomed.cas.cz
SOURCE: Progress in Brain Research, (2001) 132/- (339-363).
Refs: 94
ISSN: 0079-6123 CODEN: PBRRA4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery

Searcher : Shears 571-272-2528

016 Cancer
020 Gerontology and Geriatrics
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In conclusion, glial cells control not only ECS ionic composition, but also ECS size and geometry. Since ECS ionic and volume changes have been shown to play an important role in modulating the complex synaptic and extrasynaptic signal transmission in the CNS, glial cells may thus affect neuronal interaction, synchronization and neuron-glia communication. As shown in Fig. 2, a link between ionic and volume changes and signal transmission has been proposed as a model for the non-specific feedback mechanism suppressing neuronal activity (Sykova, 1997; Ransom, 2000). First, neuronal activity results in the accumulation of [K(+)](e), which in turn depolarizes glial cells, and this depolarization induces an alkaline shift in glial pH(i). Second, the glial cells extrude acid and the resulting acid shift causes a decrease in the neuronal excitability. Because ionic transmembrane shifts are always accompanied by water, this feedback mechanism is amplified by activity-related glial swelling compensated for by ECS volume shrinkage and by increased tortuosity, presumably by the crowding of molecules of the ECS matrix and/or by the swelling of fine glial processes. This, in turn, results in a larger accumulation of ions and other neuroactive substances in the brain due to increased diffusion hinderance in the ECS. Astrocyte hypertrophy, proliferation and swelling influence the size of the ECS volume and tortuosity around neurons, slowing diffusion in the ECS. Their organization may also affect diffusion anisotropy, which could be an underlying mechanism for the specificity of extrasynaptic transmission, including 'cross-talk' between distinct synapses (Barbour and Hausser, 1997; Kullmann and Asztely, 1998). An increased concentration of transmitter released into a synapse (e.g. repetitive adequate stimuli or during high frequency electrical stimulation which induces LTP) results in a significant activation of high-affinity receptors at neighboring synapses. The efficacy of such synaptic cross-talk would be dependent on the extracellular space surrounding the synapses, i.e. on intersynaptic geometry and diffusion parameters. Other recent studies have also suggested an important role for proteoglycans, known to participate in multiple cellular processes, such as axonal outgrowth, axonal branching and synaptogenesis (Hardington and Fosang, 1992; Margolis and Margolis, 1993) that are important for the formation of memory traces. Recent observation of a decrease of fibronectin and chondroitin sulfate proteoglycan staining in the hippocampus of behaviorally impaired aged rats (Sykova et al., 1998a,b) supports this hypothesis. It is reasonable to assume that besides neuronal and glial processes, macromolecules of the extracellular matrix contribute to diffusion barriers in the ECS. It is therefore apparent that glial cells play an important role in the local architecture of the CNS and they may also be involved in the modulation of signal transmission, in plastic changes, LTP, LTD and in changes of behavior and memory formation.

L15 ANSWER 26 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002454821 EMBASE
TITLE: The nitric oxide/cyclic GMP system in astroglial

cells.
AUTHOR: Baltrons M.A.; Garcia A.
CORPORATE SOURCE: A. Garcia, Inst. de Biotecnol. 'Villar Palasi', Depto. de Bioquim. y Biol. Molec., Universidad Autonoma de Barcelona, 08193 Barcelona, Spain. agustina.garcia@uab.es
SOURCE: Progress in Brain Research, (2001) 132/- (325-337). Refs: 144
ISSN: 0079-6123 CODEN: PBRRA4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 002 Physiology
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 27 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 7
ACCESSION NUMBER: 2001:296172 BIOSIS
DOCUMENT NUMBER: PREV200100296172
TITLE: Caspase-mediated suppression of glutamate (**AMPA**) **receptor** channel activity in hippocampal neurons in response to DNA damage promotes apoptosis and prevents necrosis: Implications for neurological side effects of **cancer** therapy and neurodegenerative disorders.
AUTHOR(S): Lu, Chengbiao [Reprint author]; Fu, Weiming [Reprint author]; Mattson, Mark P. [Reprint author]
CORPORATE SOURCE: Laboratory of Neurosciences, National Institute on Aging, 5600 Nathan Shock Drive, Baltimore, MD, 21224, USA
SOURCE: Neurobiology of Disease, (April, 2001) Vol. 8, No. 2, pp. 194-206. print.
ISSN: 0969-9961.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Jun 2001
Last Updated on STN: 19 Feb 2002

AB DNA damage in neurons is implicated in the pathogenesis of several neurodegenerative disorders and may also contribute to the often severe neurological complications in **cancer** patients treated with chemotherapeutic agents. DNA damage can trigger apoptosis, a form of controlled cell death that involves activation of cysteine proteases called caspases. The excitatory neurotransmitter glutamate plays central roles in the activation of neurons and in processes such as learning and memory, but overactivation of ionotropic glutamate receptors can induce either apoptosis or necrosis. Glutamate **receptors** of the **AMPA** (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate) type mediate such physiological and pathological processes in most neurons. We now report that DNA damage can alter glutamate receptor channel activity by a mechanism involving activation of caspases. Whole-cell patch clamp analyses revealed a marked decrease in

AMPA-induced currents after exposure of neurons to camptothecin, a topoisomerase inhibitor that induces DNA damage; N-methyl-D-aspartate (NMDA)-induced currents were unaffected by camptothecin. The decrease in AMPA-induced current was accompanied by a decreased calcium response to AMPA. Pharmacological inhibition of caspases abolished the effects of camptothecin on AMPA-induced current and calcium responses, and promoted excitotoxic necrosis. Combined treatment with glutamate receptor antagonists and a caspase inhibitor prevented camptothecin-induced neuronal death. Caspase-mediated suppression of AMPA currents may allow neurons with damaged DNA to withdraw their participation in excitatory circuits and undergo apoptosis, thereby avoiding widespread necrosis. These findings have important implications for treatment of patients with **cancer** and neurodegenerative disorders.

L15 ANSWER 28 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001244382 EMBASE
TITLE: Mechanisms of inflammatory pain.
AUTHOR: Kidd B.L.; Urban L.A.
CORPORATE SOURCE: B.L. Kidd, Reader in Rheumatology, St Bart's/Royal London Sch. of Med., Turner Street, London E1 2AD, United Kingdom
SOURCE: British Journal of Anaesthesia, (2001) 87/1 (3-11). Refs: 78
ISSN: 0007-0912 CODEN: BJANAD
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

L15 ANSWER 29 OF 33 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2000-194968 [17] WPIDS
DOC. NO. CPI: C2000-060376
TITLE: Use of inhibitor of interaction of glutamate with **alpha-amino-3-hydroxy-5-methyl-4-isoxazole**-propionate or kainate **receptor** complex for treatment of demyelinating disorders e.g. multiple sclerosis.
DERWENT CLASS: B05
INVENTOR(S): SMITH, T; TURSKI, L
PATENT ASSIGNEE(S): (EISA) EISAI CO LTD
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000001376	A2	20000113	(200017)*	EN	104
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: JP US					
EP 1100504	A2	20010523	(200130)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

JP 2002519373 W 20020702 (200246) 130

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000001376	A2	WO 1999-GB2112	19990702
EP 1100504	A2	EP 1999-929545	19990702
		WO 1999-GB2112	19990702
JP 2002519373	W	WO 1999-GB2112	19990702
		JP 2000-557823	19990702

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1100504	A2	Based on	WO 2000001376
JP 2002519373	W	Based on	WO 2000001376

PRIORITY APPLN. INFO: GB 1998-24393 19981106; GB 1998-14380 19980702

AN 2000-194968 [17] WPIDS

AB WO 200001376 A UPAB: 20000405

NOVELTY - Use of an inhibitor (I) of the interaction of glutamate with the **alpha-amino-3-hydroxy-5-methyl-4-isoxazole**-propionate (**AMPA**) **receptor** complex and of the interaction of glutamate with the kainate receptor complex in the manufacture of a medicament for treatment of demyelinating disorder (DMD) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) use of an inhibitor of interaction of glutamate with an **AMPA receptor** for treatment of demyelinating disorders;

(2) use of an inhibitor of interaction of glutamate with the kainate receptor for treatment of demyelinating disorders.

ACTIVITY - Neuroprotective; immunosuppressive.

The figure shows the effect of the **AMPA receptor** antagonist NBQX on severity of paralysis during experimental allergic encephalomyelitis (EAE) in rats, at a dose of 30 mg/kg twice daily.

MECHANISM OF ACTION - Glutamate-**AMPA** and/or kainate **receptor** complex interaction inhibitors.

USE - For treatment of DMD such as acute disseminated encephalomyelitis, acute demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, Marchifava-Bignami disease, central pontine myelinolysis, Devic syndrome, Balo disease, human immunodeficiency virus (HIV)- or human T-cell leukemia virus (HTLV)-myelopathy, progressive multifocal leucoencephalopathy or a secondary demyelinating disorder, particularly central nervous system (CNS) lupus erythematodes, polyarteriitis nodosa, Sjogren syndrome, sarcoidosis or isolated cerebral vasculitis (all claimed).

DESCRIPTION OF DRAWING(S) - The figure shows the effect of the **AMPA receptor** antagonist NBQX on severity of paralysis during EAE in rats, at a dose of 30 mg/kg twice daily.

Dwg.1/8

L15 ANSWER 30 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 8

ACCESSION NUMBER: 2001:284308 BIOSIS
DOCUMENT NUMBER: PREV200100284308
TITLE: cDNA microarray to study gene expression of dopaminergic neurodegeneration and neuroprotection in MPTP and 6-hydroxydopamine models: Implications for idiopathic Parkinson's disease.
AUTHOR(S): Mandel, S.; Grunblatt, E.; Youdim, M. [Reprint author]
CORPORATE SOURCE: Department of Pharmacology, Faculty of Medicine, Technion, 31096, Haifa, Israel
youdim@tx.technion.ac.il
SOURCE: Journal of Neural Transmission Supplement, (2000) Vol. 60, pp. 117-124. print.
CODEN: JNTSD4. ISSN: 0303-6995.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jun 2001
Last Updated on STN: 19 Feb 2002

AB cDNA microarray membranes comprising 1,200 different gene fragments have been employed to identify gene expression profile in MPTP-induced nigro striatal dopamine neurodegeneration and its protection with R-apomorphine. Both MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and R-apomorphine (R-APO) induced alterations in specific patterns of gene expression. MPTP altered the expression of 49 different genes involved in oxidative stress (oxidative stress-induced protein A 170, cytochrome P450 1A1 and Osp94), inflammation (cytotoxic cytokines, eg: **IL-1**, **IL-6**, TNF-alpha), protective cytokines (IL-10), glutamate **receptors** (NMDA but not **AMPA receptors**), neurotrophic factors (GDNF, EGF), nitric oxide synthase and transferrin receptor, as determined by microarray membrane hybridization. Furthermore, an additional cascade of further, yet undefined events, also occurred (cell cycle regulators and signal transduction factors), that might act in parallel to oxidative stress (OS) and inflammation, to converge eventually into a common pathway leading to neurodegeneration. R-APO, previously shown by us to protect against MPTP neurotoxicity, prevented the over expression of several genes known to participate in cell death. cDNA microarrays will provide new prospects to study and identify various mechanism of neurodegeneration and neuroprotection not feasible with conventional biochemical procedures, as well as new prospects to develop effective neuroprotective drugs.

L15 ANSWER 31 OF 33 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:135242 BIOSIS
DOCUMENT NUMBER: PREV200100135242
TITLE: Glutamate antagonists limit **tumor** growth.
AUTHOR(S): Rzeski, W. [Reprint author]; Turski, L.; Ikonomidou, C.
CORPORATE SOURCE: Charite Children's Hospital, Humboldt University, Berlin, Germany
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26,

No. 1-2, pp. Abstract No.-784.7. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Mar 2001
Last Updated on STN: 15 Feb 2002

AB Glutamate is an essential amino acid and a transmitter in the mammalian nervous system. N-Methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate (**AMPA**)/kainate and metabotropic **receptors** are activated by glutamate. Glutamate serves trophic functions during development of the nervous system and controls neuronal proliferation, migration, differentiation, plasticity, and survival. Whether and how glutamate influences **tumor** growth is not known. We show that glutamate NMDA and AMPA antagonists inhibit proliferation of neuroblastoma, medulloblastoma, astrocytoma, lung, thyroid, breast and colon **carcinoma** cells in vitro. The antiproliferative effect of glutamate antagonists results from decreased cell division and increased cell death, and is reduced by Ca2+-deprivation. Furthermore, the NMDA antagonist dizocilpine and the AMPA antagonist GYKI52466 enhance tumoricidal effect of cytostatic drugs **cyclophosphamide, cisplatin,** thiotepa and vinblastin, produce morphological alterations in **tumor** cells consisting of reduced membrane ruffling and pseudopodial protrusions, and decrease their motility and invasive growth. Suppression of **tumor** growth by glutamate antagonists was also achieved in human **tumor** xenografts in nu/nu and SCID-mice in vivo. These observations suggest novel therapeutic use for glutamate antagonists in the treatment of **cancer**.

L15 ANSWER 32 OF 33 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 2000032190 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10564345
TITLE: Potentiation of glutamatergic agonist-induced inositol phosphate formation by basic fibroblast growth factor is related to developmental features in hippocampal cultures: neuronal survival and glial cell proliferation.
AUTHOR: Blanc E M; Jallageas M; Recasens M; Guiramand J
CORPORATE SOURCE: Laboratoire de Plasticite Cerebrale, CNRS EP628, Universite Montpellier II, France.
SOURCE: European journal of neuroscience, (1999 Oct) 11 (10) 3377-86.
Journal code: 8918110. ISSN: 0953-816X.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991208

AB We investigated the modulation by growth factors of phospholipase C (PLC)-linked glutamate receptors during in vitro development of hippocampal cultures. In defined medium, glial cells represent between 3 and 14% of total cell number. When we added basic fibroblast growth factor (bFGF) 2 h after plating, we found: (i) a neuroprotection from naturally occurring death for up to 5 days; (ii) a proliferation of glial cells from day 3; and (iii) a potentiation of quisqualate (QA)-induced inositol phosphate (IP) formation from 1 to 10 days in vitro (DIV) and 1S, 3R-amino-cyclopentane-1,3-dicarboxylate (ACPD) response from 3 to 10 DIV. The antimitotic cytosine-beta,D-arabinofuranoside (AraC) blocked glial cell proliferation induced by bFGF, but not neuroprotection. Under these conditions, the early potentiation of the QA response (1-3 DIV) was not changed, while the ACPD and late QA response potentiations were prevented (5-10 DIV). Epidermal growth factor was not neuroprotective but it induced both glial cell proliferation and late QA or ACPD potentiation. Surprisingly, the early bFGF-potentiated QA-induced IP response was blocked by 6, 7-dinitro-quinoxaline-2,3-dione (DNQX), suggesting the participation of ionotropic (RS)-**alpha**-**amino**-3-**hydroxy**-5-**methyl**-4-**isoxazolepropionate** (**AMPA**)/kainate (KA) **receptors**. The delayed bFGF-potentiated ACPD-induced IP response is inhibited by (S)-alpha-methyl-4-carboxyphenylglycine (MCPG), indicating possible activation of glial metabotropic receptors. These results suggest that, in hippocampal cultures, bFGF modulates **AMPA** and metabotropic glutamate **receptors** linked to the IP cascade, possibly in relation to the regulation of neuronal survival and glial cell proliferation, respectively.

L15 ANSWER 33 OF 33 JICST-EPlus COPYRIGHT 2004 JST on STN

ACCESSION NUMBER: 970791104 JICST-EPlus

TITLE: Neurotrophic factors using neuro-circuit simultaneous multiplepoint analysis and development of functional evaluation of modulators. (Human science promotion foundation S).

AUTHOR: INOUE KAZUHIDE
TABUCHI MASAHIRO
YAMAGUCHI TOKIO
KURODA YOICHIRO
KUMAKURA KONOSUKE
SHIBATA SHIGENOBU

CORPORATE SOURCE: National Inst. of Hygienic Sciences
Tsumura
Yamanouchi Pharm. Co., Ltd.
Tokyo Metrop. Inst. for Neurosci.
Life Sci. Inst. Sophia Univ.
Waseda Univ., Sch. of Hum. Sci.

SOURCE: Kanmin Kyodo Purojekuto Kenkyu Hokoku. Heisei 8 Nendo. Dai5 Bun'ya. Kenko Hoji no Kiso to shiteno Seitai Bogyo Kiko no Kaimei, (1997) pp. 279-287. Journal Code: N19972029 (Ref. 19)

PUB. COUNTRY: Japan

DOCUMENT TYPE: Journal; Article

LANGUAGE: Japanese

STATUS: New

Searcher : Shears 571-272-2528

AB 1) This paper describes the relationships between a new neurotransmitter, ATP, and zinc ion. The unusual metal, zinc ion, is found in the hippocampal system at high concentrations and is released by stimulation.Zinc ion increases the reaction by acting on an ion-channel type ATP receptor, and specifically suppresses the reaction by acting on CCE in the post-stimulation of G-protein binding receptor.2) The primary culture system of the monkey cerebral cortex nerve cell was established.3) A search for the factor controlling the kinetics of the neurotransmitter release, and an analysis of the mechanism of action, have identified a new indicator for functional evlauation of the modulator.4) In studies on a delayed nerve cell necrosis model system, YM872 has been found to be a highly water soluble competitive antagonist for **AMPA receptor** and it has a protective action for nerve cells.5) A Chinese drug, which shows inhibitory action on nerve cell death in the SCG test, may be an effective treatment for the diabetic peripheral nerve disorder in the model.6) Studies on the biological clock, using a section of the suprachiasmatic nucleus of a GFAP gene deficient mouse, indicates that the system may be useful for elucidating the nerve mechanism involved in photosynchronization of the biological clock.

FILE 'HOME' ENTERED AT 09:55:02 ON 14 APR 2004